FOOD AND DRUG ADMINISTRATION

CENTER FOR TOBACCO PRODUCTS

TOBACCO PRODUCTS SCIENTIFIC ADVISORY COMMITTEE

(TPSAC)

Thursday, July 21, 2011

1:00 p.m. to 5:15 p.m.

Afternoon Session

9200 Corporate Boulevard

Rockville, Maryland

This transcript has not been edited or corrected, but appears as received from the commercial transcribing service.

Meeting Roster

Dissolvable Tobacco Products Session

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C O N T E N T S

C O N T E N T S (continued)

P R O C E E D I N G S

(1:07 p.m.)

Call to Order

DR. SAMET: Good afternoon. We're going to go ahead and get started, if everyone could take their seats, please.

We now have left the topic of menthol behind and we are moving on to the issue of dissolvable tobacco products and public health.

So as you know, we're getting started on the process for our required report to the Secretary of Health and Human Services regarding the issue of the nature and impact of the use of dissolvable tobacco products on the public health, including such use among children.

Let me turn to Caryn for the conflict of interest statement.

Conflict of Interest Statement

MS. COHEN: The Food and Drug Administration is convening this afternoon's meeting of the Tobacco Products Scientific Advisory Committee

under the authority of the Federal Advisory Committee Act.

With the exception of the industry representatives, all members and non-voting members are special government employees or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

The following information on the status of this committee's compliance with the federal ethics and conflict of interest laws, covered by, but not limited to, those found at 18 USC Section 208 and Section 712 of the Federal Food, Drug, and Cosmetic Act, is being provided to participants in today's meeting and to the public.

FDA has determined that members of this committee are in compliance with federal ethics and conflict of interest laws. Under 18 USC Section 208, Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have potential financial conflicts when it is determined that the agency's need for a particular individual's services outweighs his or

her potential financial conflict of interest.

Under Section 712 of the FD&C, Congress has authorized FDA to grant waivers to special government employees and regular federal employees with potential conflicts when necessary to afford the committee essential expertise.

Related to the discussions of today's meeting, members of this committee have been screened for potential financial conflicts of interests of their own, as well as those imputed to them, including those of their spouses or minor children, and, for purposes of 18 USC Section 208, their employers. These interests may include investments, consulting, expert witness testimony, contracts, grants, CRADAs, teaching, speaking, writing, patents and royalties, and primary employment.

Today's agenda involves the nature and impact of the use of dissolvable tobacco products on public health. These discussions will begin the process for TPSAC's required report to the Secretary of Health and Human Services regarding

the issue of the nature and impact of the use of dissolvable tobacco products on public health, including such use among children. This is a particular matters meeting during which general issues will be discussed.

Based on the agenda for today's meeting and all financial interests reported by the committee members, no conflict of interest waivers have been issued in connection with this meeting. To ensure transparency, we encourage all committee members to disclose any public statements they have made concerning the issues before the committee today.

With respect to FDA's invited industry representatives, we would like to disclose that Drs. Daniel Heck and John Lauterbach and Mr. Arnold Hamm are participating in this meeting as non-voting industry representatives, acting on behalf of the interests of the tobacco manufacturing industry, the small business tobacco manufacturing industry, and tobacco growers, respectively.

Their role at this meeting is to represent

these industries in general and not any particular company. Dr. Heck is employed by Lorillard Tobacco Company; Dr. Lauterbach is employed by Lauterbach & Associates, LLC; and, Mr. Hamm is retired.

FDA encourages all other participants to advise the committee of any financial relationships that they may have with any firms at issue.

I'd like to remind everybody here to turn off your cell phones completely because they interfere with the sound system. If you're calling in, Dr. Clanton, please keep your phone on mute unless you are speaking.

I would also like to identify the FDA press contacts, Michelle Bolek and Jeff Ventura, if you're here.

Thank you.

Introduction of Committee Members

DR. SAMET: Thank you. I think because we do have new committee members, we might take a moment longer in the introductions, just so everybody has a better sense of who's around the table and what we do.

Again, I'm Jon Samet. I'm the chair of the Department of Preventive Medicine and head of the Institute for Global Health at USC, and my background is internal medicine, pulmonary medicine, and epidemiology.

Karen?

MS. DELEEUW: Karen DeLeeuw, and I am from the Colorado Department of Public Health and Environment, and I ran the tobacco control program there for many years.

DR. BENOWITZ: Neal Benowitz, University of California, San Francisco. I'm professor of medicine and chief of clinical pharmacology. I'm an internist and I practice cardiology. My research over the years has been focused mostly on the human pharmacology of nicotine, including cardiovascular effects, metabolism, genetic factors, biomarkers, et cetera.

DR. SIMONS-MORTON: I'm Bruce Simons-Morton. I'm the chief of the prevention research branch at the National Institutes of Child Health and Human Development at the National Institutes of Health,

where I direct a program of research on adolescent health behavior, including the prevention of substance use among adolescents.

DR. PAMPEL: My name is Fred Pampel. I'm at the University of Colorado at Boulder. I'm a sociologist and demographer, with interests in the social determinants of smoking, and I've done studies about cohort changes in these determinants and across national differences in the determinants of smoking.

DR. NEZ HENDERSON: Good afternoon. My name is Patricia Nez Henderson. I'm the vice president for the Black Hills Center for American Indian Health, a nonprofit organization. For the past 11 years, my work as focused on addressing tobacco control and prevention in native communities.

DR. BALSTER: My name is Robert Balster. I'm the director of the Institute for Drug and Alcohol Studies and a professor of pharmacology at Virginia Commonwealth University. I'm more of a drug abuse expert and have done work in behavioral pharmacology and in abuse liability assessment. I

am also currently co-director of the Virginia statewide Virginians for Healthy Youth, a funded statewide research coalition called the Virginia Youth Tobacco Project.

DR. SAMET: Okay. Dan?

DR. HECK: I'm Dan Heck, with the Lorillard Tobacco Company, representing the tobacco manufacturers. I have a background in pharmacology and toxicology and a special interest, besides tobacco products, in inhalation toxicology and the toxicology of flavoring materials.

DR. LAUTERBACH: I'm John Lauterbach, Lauterbach & Associates, representing the interests of the small business tobacco manufacturers. Lauterbach & Associates provides chemistry and toxicological and operations support to those in the tobacco industry and others interested. And before that, I was with Brown & Williamson Tobacco R&D for 24 years.

MR. HAMM: I'm Arnold Hamm, representing U.S. tobacco growers. I'm currently retired, but I was former CEO of what was known as Flue-Cured

Tobacco Cooperative Stabilization Corporation.

DR. DJORDJEVIC: I'm Mirjana Djordjevic with the National Cancer Institute, representing the National Institutes of Health. My background is in chemistry, and currently I'm working as a program director and project officer at the Tobacco Control Research Branch.

MS. SHELTON: Hello. My name is Dana Shelton. I work with the Office on Smoking and Health at the Centers for Disease Control, and today I'm representing Dr. Tim McAfee.

DR. EVANS: Hello. I'm Sarah Evans. I'm a behavioral scientist with the Center for Tobacco Products, and I'll be the scientific lead for this topic.

DR. ASHLEY: And I am David Ashley. I am director of the Office of Science here at the Center for Tobacco Products.

DR. SAMET: Okay. And, Mark, not forgotten.

DR. CLANTON: Mark Clanton, pediatrician, former deputy director of the National Cancer Institute.

DR. SAMET: Okay. Welcome, to the new members around the -- new faces around the table, doing a lot of work together, I'm sure.

We're going to move on to the first FDA presentation. I guess, David, you're going to do that.

FDA Presentation - David Ashley

DR. ASHLEY: Thank you and welcome this afternoon to our opening session for the third topic that the Tobacco Products Scientific Advisory Committee is addressing.

First, a disclaimer. The information in these materials is not a formal dissemination of information by FDA and does not represent agency position or policy. The information is being provided to TPSAC to aid the committee in its evaluation of the issues and questions referred to the committee.

First, I'm going to give you the charge, as we see it right now. According to the statute, the Tobacco Products Scientific Advisory Committee is required to review and provide recommendations to

FDA regarding the nature and the impact of the use of dissolvable tobacco products on the public health, including such use among children.

In its deliberations, TPSAC is to consider the risks and benefits to the population as a whole, including users and non-users of tobacco products, of the proposed standard; the increased or decreased likelihood that existing users of tobacco products will stop using such products; and the increased or decreased likelihood that those who do not use tobacco products will start using such products. The TPSAC report and recommendations are due March 23rd, 2012.

We do have certain definitions that are available to us in the statute. That includes for what is a tobacco product. And a tobacco product is any product that's made or derived from tobacco that is intended for human consumption, including any component, part, or accessory of a tobacco product, except for raw materials, other than tobacco, used in manufacturing of component, part or accessory of a tobacco product. It does not

mean a product that is a drug, a device, or a drug-device combination product.

So we do have a definition for tobacco product.

Regulated tobacco products, currently, cigarettes, cigarette tobacco, smokeless tobacco, and roll-your-own tobacco are subject to regulation under Chapter 9. FDA intends to propose a regulation that would deem products meeting the statutory definition of tobacco product found in Section 201(rr) of the FD&C Act to be subject to FDA's jurisdiction. So this is the deeming rule.

We also have a definition for smokeless tobacco. Smokeless tobacco is any tobacco product that consists of cut, ground, powdered or leaf tobacco and that's intended to be placed in the oral or nasal cavity. But we do not have currently a statutory definition of dissolvable tobacco product. That is not in the statute.

We believe that many dissolvable tobacco products meet the current statutory definition of smokeless tobacco. It's also possible that some

dissolvable tobacco products are not currently regulated under Chapter 9 of the Tobacco Control Act.

The meeting topics that we will be discussing, the topic is, specifically, dissolvable tobacco products. It's not smokeless tobacco, in general. The statute clearly indicates that the charge to the committee is to look at dissolvable tobacco products.

Also, TPSAC is not being asked to address the use of dissolvable tobacco products as cessation aids. In other words, we're not being asked to address dissolvable products for use as a drug. They're not being asked whether specific products are substantially equivalent to products which were on the market on February 15th, 2007. We have a process in place to deal with that.

TPSAC is also not being asked at this time to evaluate individual applications. At some time, those applications will be referred to TPSAC. They may be referred to TPSAC, and we will deal with those at that time. So we're not looking at

individual applications.

TPSAC is also not being asked to address the use of dissolvable tobacco products as potential modified risk tobacco products. Again, that is a very product-specific question, and we will deal with those with TPSAC when that time comes.

FDA has planned a public workshop on this issue in August, and the Institute of Medicine is also currently considering this issue; that is the issue of modified risk tobacco products.

Continuing a little bit more on the meeting topics, in reviewing the nature and the impact of the use of dissolvable tobacco products on public health, FDA requests that TPSAC be inclusive, without regard to whether they are currently regulated. And so we don't want you to be limited to products that meet the definition of smokeless tobacco. We're wanting TPSAC to be broad in their look at the question of dissolvable tobacco products. And in providing recommendations to FDA, we request that TPSAC identify the types of dissolvable tobacco products to which the advice

does and does not apply.

Today, what we're going to be seeing are industry presentations, and so I want to give you a little bit of background on where that comes from.

Manufacturers which FDA had reason to believe were marketing dissolvable tobacco products as of June 2011 were invited to voluntarily present at today's TPSAC meetings. Presentations are voluntary, and they were intended to give industry an opportunity to inform TPSAC.

For today's session, Altria Client Services declined to present. R.J. Reynolds accepted and Star Scientific accepted. If other manufacturers who make a dissolvable tobacco product are identified, they may be invited to speak at future TPSAC meetings.

The focus of the industry presentations, what we sent out to the industry and asked them to present for today and tomorrow's sessions, is looking at three topics. And we asked -- and we're presenting these by topic as opposed to by company. Those three topics are the marketing and consumer

perception, abuse liability and health risks, and initiation and cessation.

FDA requested that each company present industry data and peer-reviewed literature relevant to each of those three topics. FDA also asked that each company submit a background package to the committee with more detailed information on these same topics.

The first topic -- let me break the topics down a little bit more so you'll understand specifically what we asked industry to present, again, at this afternoon's and tomorrow's meeting.

As far as marketing and consumer research, we asked for a description of dissolvable tobacco products that your company has marketed or plans to market; marketing and segmentation strategies for dissolvable tobacco products; description of how the products are designed, manufactured and marketed to reach the target market; perception and use of dissolvable tobacco products by children and adolescents; and, even in the absence of test data, any properties which might make these products more

or less attractive to children and youth.

As far as topic 2 is concerned, that's, again, abuse liability and health risks, we asked the companies to talk about abuse liability of dissolvable tobacco products, including the product design, the quantity and form of nicotine, pharmacokinetics of nicotine, potential impact on non-targeted populations. Also, we asked them to discuss the efforts to limit or reduce abuse liability.

We asked them to discuss the safety profile of dissolvable tobacco products, including available information on both local and systemic adverse health effects which are specific to dissolvable products; and, finally, the risks associated with accidental ingestion of dissolvable products by children.

The third topic is around initiation and cessation. And so we asked them to talk about whether dissolvable tobacco products might be used as starter products for non-users and how the composition and design features impact the use by

non-tobacco product users.

We asked them to talk about the likelihood that users of tobacco products will completely switch to dissolvable tobacco products as opposed to a pattern of dual use; and, finally, the likelihood of dissolvable tobacco products users quitting tobacco consumption in comparison to users of other tobacco products.

I'd be glad to try to address any clarifying questions.

DR. SAMET: David, if you could go back to the fourth slide.

DR. ASHLEY: Fourth?

DR. SAMET: Yes. I just want to make sure I understand, because I went back to through the risks and benefits of the proposed standard. Help me with that.

DR. ASHLEY: I believe that shouldn't actually -- I believe that's a typo, Jon.

DR. SAMET: Okay. That's fine.

DR. ASHLEY: Yes. When I got to it myself, I realized that was not what -- it should have

stopped at "tobacco products."

DR. SAMET: Okay. Thank you. I thought I had missed something there.

DR. ASHLEY: I think that was a copy from something else.

DR. SAMET: Okay.

Neal?

DR. BENOWITZ: David, the first statement, you said we're not supposed to consider individual applications, like, for harm reduction and things like that. But the first sentence, obviously, includes that, because if you're looking at any benefit, you're looking at what is the societal benefit, which would be either smoking fewer cigarettes or quitting. Those are specific sort of uses or applications.

How can we not consider that?

DR. ASHLEY: We're not going to be bringing specific applications to you on a particular product. I mean, that's going to be a very -- and we may do that later. At a later time, when we have applications we want to bring to the TPSAC, we

may be bringing specific applications to you.

So this session now is not to look at individual applications.

DR. BENOWITZ: Okay.

DR. ASHLEY: But the concept --

DR. BENOWITZ: But our charge is just to look at --

DR. ASHLEY: The concept is looking at dissolvable tobacco products as a whole, yes. But, again, it's not the time yet for individual applications.

DR. SAMET: Patricia?

DR. NEZ HENDERSON: Are we going to address during this time the epidemiology of dissolvables, or is that at a later time?

DR. ASHLEY: I think the epidemiology, as it fits into the questions that we pose -- again, this is a series of meetings, so if there are additional topics you would like to be presented on, we can do that. But as epidemiology fits into those other questions, and I think it fits, to a large degree, into some of those other questions, yes, that can

be addressed.

DR. SAMET: Mark, anything?

[No response.]

DR. SAMET: So I guess Karen is next.

FDA Presentation - Karen Templeton-Somers

DR. TEMPLETON-SOMERS: Hi. I'm Karen Templeton-Somers, and I'm the team leader for the group in the Office of Science that manages the Tobacco Products Scientific Advisory Committee. I'm going to take just a few minutes here to explain the process that we'll be using for the production of the second TPSAC report, the one on dissolvable tobacco products.

As you're aware, the Family Smoking Prevention and Tobacco Control Act requires the TPSAC to submit a report and recommendations on the topic of the nature and impact of the use of dissolvable tobacco products on the public health, including such use among children.

This report and recommendation are due no later than two years after the establishment of TPSAC or on March 23rd, 2012. We'll be holding

three or four meetings on this topic between today and March 2012. FDA will be creating detailed minutes and verbatim transcripts of the proceedings of each meeting. These will be available for review before the next meeting, along with the other meeting materials.

The report and recommendations from the TPSAC on the topic of dissolvable tobacco products will then be the compilation of the minutes and the other materials from the TPSAC meetings on the topic. Because this report and recommendation will largely be developed in the open sessions of TPSAC, the contributions of the industry representatives to those sessions will be included.

Any questions?

DR. SAMET: I think just to clarify, and, again, just going back to discussions, you are not anticipating a report that looks like the menthol report, in a sense.

DR. TEMPLETON-SOMERS: We are not.

DR. SAMET: So go back to your plans for developing the report and let's just --

DR. TEMPLETON-SOMERS: We are not anticipating that type of document.

DR. SAMET: Right. So we may offer up something that may be in addition to compiling those transcripts and other materials. I think that probably remains to be seen. But you are not anticipating a --

DR. TEMPLETON-SOMERS: We are not anticipating a writing subcommittee and writing groups.

DR. SAMET: Right. Okay. So I just wanted to make that clear. But, I mean, that said, the report may, in the end, need something that looks like a report, compiled minutes, transcripts, and other materials; that that would be the foundation, in a sense, for it.

DR. TEMPLETON-SOMERS: Yes.

DR. SAMET: Okay.

Neal?

DR. BENOWITZ: Just to follow-up with that. I assume that there will be specific questions and conclusions that the committee will provide.

DR. TEMPLETON-SOMERS: Yes. We expect that we'll have detailed and appropriate questions, especially at the last meeting, which will be the penultimate, I guess, of it.

DR. BENOWITZ: As Jon said, that probably will require some organization of the data that we've reviewed and documentation of support for our conclusions.

DR. TEMPLETON-SOMERS: It could, yes. We'll see as to how it goes, but it's a little -- we just have a procedure which is reasonably common in other centers to use the actual meeting minutes or summaries of the meetings as the report and recommendations to the agency.

DR. SAMET: Okay. I think this will become clearer when it needs to.

DR. TEMPLETON-SOMERS: I think it will, yes.

DR. SAMET: Okay. We hope.

Other questions? I think this, among other things, may free us from the rather large burden that we had of writing. On the other hand, at least from the initial materials provided, there's

less to write about at this point, as well.

Good. I guess we'll move on then to the industry presentations. Initially, the first topic that David introduced, marketing and consumer perception, we're going to hear first from Curtis Wright from Star Scientific. And thank you for coming to speak with us.

Industry Presentation - Curtis Wright

DR. WRIGHT: Thank you; a pleasure to be with you. I'm going to follow the outline that we were earlier given, but I'm going to have to move quickly, because I don't have much time and I have too many slides.

There is no agreed-upon definition of what a low nitrosamine tobacco product is, but for the purposes of this talk, we'll use the current WHO recommendations of 2 parts per million dry weight.

Low nitrosamine tobacco is not new. It was used as the major form of tobacco in the 19th century in America. But as you can see, the introduction of the machine-produced cigarette wiped out smokeless tobacco use in this country.

It's less than 10 percent of cigarette usage.

Unfortunately, the introduction of the cigarette also resulted in a robust epidemic of lung cancer, which neatly tracks, after a 25-year latency lag, the introduction of the cigarette. There are 443,000 deaths a year attributed to smoking by the CDC, and they're split among cardiovascular, cancer, and pulmonary disease. This has some implications, because if a smoke product could be made that could cut the risk of lung cancer in half, that still would leave a considerable pulmonary and cardiovascular mortality.

Star Scientific, as a matter of policy, as advised by its scientific advisory board, believes that attempting to reduce the surface active respirable particles and their mortality from a combusted product is not achievable with current technology.

The reason for this is that Star actually made a low nitrosamine cigarette, took it to its internal scientific advisory committee, and that

committee recommended that they not make the product, and Star got out of the cigarette business.

What you see here is some work by Pope looking at smokers, secondhand smoke, and environmental smoke in terms of respirable particles and cardiovascular risk. The thing to note for this plot is that the X-axis is logarithmic. To materially reduce cardiovascular risk by reducing smoke particle inhalation, you have to take it down a factor of 10 or more. We just don't know how to do that with a combusted product yet. We don't. We don't know what the rest of the industry can do.

There are three classes of tobacco products that were either developed to deliver less toxins to the user or have been shown to deliver less toxins to the user: low nitrosamine chewing tobacco, Swedish Snus, and dissolvable tobacco products.

Smokeless tobacco, as most of you know, contains specific known measurable toxins, and

those toxins, as cited by the Surgeon General, center around tobacco-specific nitrosamines, volatile nitrosamines, various polycyclic aromatic hydrocarbons, and polonium-210.

Since the carcinogen content of smokeless tobacco was as high or higher than smoke tobacco at the time that report was written, there was a recommendation made that smokeless tobacco not be considered to be of lower risk than smoke tobacco.

The American Cancer Society has done about 25 to 35 years of work on tobacco-specific nitrosamines and has nicely shown in population-based studies, that the amount of nitrosamine that you put in your mouth rather nicely predicts the amount of nitrosamine that's excreted in the urine, nitrosamine metabolites, NNAL, and that it's proportional, and that lower nitrosamines in products would lead to lower exposure of the user.

Concern about TSNAs and smokeless tobacco products is appropriate and rational and very real. There is an extraordinary range of nitrosamine content, ranging from the ethnic products of the

Sudan, which have 3 million parts per billion, to conventional U.S. dry snuff, which is about 168,000 parts per billion; U.S. moist snuff, which is about 13,000 parts per billion; Swedish Snus, which ranges anywhere from 5,000 to 1,000 parts per billion; and, the Star low TSNA products, which we'll talk about.

TSNAs are important, and they have been important for at least a decade or more. John Slade specifically called -- and I'm delighted to be here because he called, along with Jack Henningfield, for the FDA to set specific ceilings for yields of tobacco-specific nitrosamines.

So far, the response has been lukewarm. Dr. Stepanov and her coauthors said it as well as anybody could in 2011, "Despite the available knowledge and tools to reduce TSNA content in cigarette tobacco, the levels of TSNA in the tobacco filler are essentially the same as those reported 30 years ago."

Star developed dissolvable tobacco products beginning in 1990. They had developed a new

process for reducing the tobacco-specific nitrosamine content from parts per million in the tobacco feedstock to parts per billion.

The first product, Ariva, was the 240 milligram dissolving lozenge, because one of the goals of the product was that female smokers would use it. Star was successful in lowering nitrosamines. The products were not toxin-free, but they had certainly much lower TSNAs.

As you can see, this is a logarithmic axis on the Y-axis, and you can see that we go from dry snuff down to dissolvables, and we have three orders of magnitude or more reduction.

Dissolvable tobacco is not NRT. NRT is a drug. NRT treats disease. NRT is taxed and handled as a pharmaceutical. Dissolvable tobacco is a tobacco product, taxed, made and handled as such.

What is in a dissolvable product? Powdered, low TSNA -- I'm talking about our products now -- powdered, low TSNA tobacco, dissolvable binders, non-cariogenic sugars, pH buffers, natural

and artificial flavors. The tobacco is ground to about .125 millimeter. It's small enough not to feel excessively granular in the mouth, but it is definitely a visible particle. Dissolvable is scientifically incorrect because the lozenge dissolves in the mouth, but the tobacco stays as a powder, which is then swallowed.

Source of the tobacco, nongenetically-altered conventional Virginia Bright, grown in Virginia by Virginia farmers, taxed in Virginia, managed in Virginia.

It is an agricultural process. It is not a synthetic process. And producing low TSNA tobacco requires the hand of a farmer. What you see here is the cumulative distribution function for the TSNA content for each of the different drying boxes in the tobacco barn.

Tobacco is taken from the field, put in the box. The box is put in the barn. The barn is closed up, and the tobacco is cured. Each box contains tobacco that may be thicker or thinner or more tightly packed or more loosely packed, and you

get variation.

As you see here, you have some trays in some boxes in the barn that have 20 parts per billion. You have some that have 200. We test box by box.

This is the manufacturing process. It's very straightforward. You contract with a specific farmer, because you first have to convince them not to put as much nitrate as the Department of Agriculture recommends on their croplands. Then you have to cure it -- grow it, cure it, keep the cured product cold, test it, reject the bad boxes, grind it, sterilize it if you're going to hold it for a prolonged period of time, store it cool, add excipients, granulate, press the lozenges, coat, test the final lozenges.

Batch-to-batch consistency is pretty good. For an agricultural product to have a level of 23 and a standard deviation of 22 for something you're measuring at the parts per billion level, that's nice control.

Tobacco, conventional tobacco, especially conventional tobacco stored moist, will form more

nitrosamines as it ages. This material does not. As you can see here, these are some lots that were held for a year and showed no increase in TSNA content.

Some tobacco products and some smokeless tobacco products that contain considerable moisture continue to form TSNAs in the can. What you see here are samples that were held at room temperature, incubator, refrigerator or freezer for a year, and they are essentially identical in TSNA content.

The analytical methods used by the company are the standard analytical methods used by most tobacco laboratories. The only caution I will give you is that dissolvable tobacco products need to be tested by the CDC method. The Health Canada method has interference from the flavorants and will give you falsely low nicotine readings.

Star is not the only one who has tested their products. Dr. Stepanov and her colleagues tested Ariva and Stonewall, and they found similar results, and they found them to be the lowest

nitrosamine products that you can currently purchase.

Star was successful in making two tobacco products, Ariva and Stonewall, which have the lowest TSNA content of any SLT product by internal, external, and independent third-party analyses. The flavors, packaging, and nicotine loading will be discussed in the abuse liability section, but they were chosen specifically to minimize the health risk, abuse risk, pediatric risk, and initiation by non-users.

Market strategy. Within a few days, I believe, of the product being announced, citizens petitions were filed objecting to the product as either an unapproved nicotine replacement therapy drug product or as a potentially harmful product to children. Neither charge was true, but Star's intended customers were smokers in their 40s and 50s, and it was clear that how Star marketed the product and where Star marketed the product were an essential part of its safety profile. We believe that today.

Star started with the nicotine. Ariva is a 1 and a half milligram lozenge; Stonewall is a 4 milligram lozenge. The amount of nicotine, on a combination of both the loading and the pH, is the major determinant of how aversive the product is to a non-tolerant user.

Cigarettes deliver nicotine to the lungs. SLT products deliver it to the mouth, and if you have enough nicotine to satisfy the user, this will cause a mouth burn. It will also cause, in the non-tolerant individual, nausea, dyspepsia, and hiccups. I grew up in the country and every kid learned this about 13 behind the barn when they tried an SLT product for the first time.

Nicotine loading, we tested it in cigarette smokers and smokeless tobacco users. Cigarette smokers preferred somewhere in the neighborhood of 1.5 milligrams of nicotine. Smokeless tobacco users wanted the larger 4 milligram nicotine lozenge.

Our behavioral consultants at the time strongly recommended that the loading be above at

least a milligram to make the product aversive to the non-tolerant user. Star loaded them, as we showed, in flavors that we thought were not attractive to children.

These are the flavors. The original flavor is the wintergreen flavor, the large blue segment. And then they then added a mint. And after the product had been on the market for about five years, they added cinnamon, java and citrus. We get repeated calls for fruit flavors. We have chosen not to do any fruit flavors. We think they are too attractive to children.

The package was designed to look like a cigarette pack, and it was designed to ensure that it did not have very attractive graphics, and I think we succeeded beyond our wildest expectations.

[Laughter.]

DR. WRIGHT: The product sleeve -- and we have samples available to the committee, which I ask that you avail yourself of -- were designed to be child-resistant. It's a typical child-resistant inner package.

The material is placed in the store in with the tobacco products. The point of sale materials are all text, except for a picture of the product, and have no attractive graphics. The stores where the product was placed were places where people bought cigarettes, Rite Aid, Holiday, Food Lion, something called Come-and-Go. I'm not from the south, so I do not know about Come-and-Go convenience stores. And smoker-friendly tobacco shops.

Promotion was limited to point of sale materials, detailing the store owners, managers and chains, and presentations at tobacco industry and retailer-related conferences. Star endorsed no youth activities and did no sampling. And we were fortunate in that independent researchers have looked at Star's marketing practices.

Caraballo conducted a series of focus groups, which I believe the CDC representative would certainly know about, and discovered that people learned of products like this from advertising, family or friends, tried them to lower

their risk or through curiosity as to what they were, and, frankly, most didn't like them.

O'Hegarty conducted a study of prep marketing techniques and concluded that the same elements that governed general tobacco marketing governed prep promotion; color, attractiveness, layout, images, message, health implications, good-looking, healthy, young people using the product, same thing.

Parascandola used the tobacco use supplement of the current population survey to study prep use, and prep use was low, more common among daily smokers, 25 to 30-year-olds, nicotine-dependent smokers, smokers who had made multiple quit attempts, and in states where PREPs were marketed.

Slater looked at Star's marketing program in a study of Ariva and Omni and found that Ariva was marketed in drugstores and urban and suburban stores in the northeast and south, the stores with predominantly white customers, black customers, via in-store advertising only, and in very few of the stores sampled.

Here is probably the most telling slide. This is what happened after launch. This is data from the Euromonitor International smokeless tobacco report. In 2009, there were 37,000 metric tons of smokeless tobacco sold in the United States, 12,000 metric tons of chewing tobacco, 200 metric tons of Swedish-style snus, 100 metric tons of dry snuff, and 17 pounds of dissolvables.

From the perspective of smokeless tobacco use in the United States, two things are obvious. The first is that there has not been a robust uptake of this product over 10 years of marketing; and, the second is in terms of the health of the American population, dissolvable tobacco is a rounding error.

Who buys it? Male, female, about the same as for other smokeless tobacco products, ages 20 -- 40 to 50, employed and retired, incomes $25,000 to $60,000 a year. Most of them have smoked for over 10 years. They're smoking a pack to two packs a day. Their self-reported statements, unverified, are that they're smoking a

lot less, a little less, or about the same, or they're dipping smokeless tobacco a lot less, a little less, or about the same.

The median usage is 3 to 5 units a day, and they use it all the places you can't smoke, at work, at home, in restaurants and bars, around children, and in the car. Their self-reported reason for using, 30 percent, they say they use it in a nonsmoking area, 23 percent switched to it, 16 percent are trying to cut down, 19 percent are trying to quit, and 11 percent enjoy dual use. They learned of the product through their friends or store display or advertising. And that's the user of Ariva and Stonewall.

Star's efforts to make the product look like a package of cigarettes, put it in a child-resistant package, put a warning on it, keep it away from children and adolescents, and refusing, frankly, to discuss the product with people who wanted to know about it who weren't already smokers, were reasonably successful. In 10 years of marketing, despite the placement of a contact

number on the package, we received zero reports of uptake or abuse by children and adolescents. And we'll discuss this further in presentation 2 on safety.

Other companies, I'll let them speak for themselves since one showed up. But most PREPs that were introduced are either hard to find now or off the market. Star's dissolvable products appeal to middle-aged smokers with long smoking histories who have tried to quit multiple times and failed.

There has not been any significant adolescent or young adult uptake. Frankly, they have not been terribly profitable products for the company to date, but we make them because it's the right thing to do.

Star started from the premise shared by experts in the field that low nitrosamine oral tobacco products could be made that posed much less risk to the user than smoking cigarettes. Star designed the products to appeal to adult smokers. They marketed the product to appeal to adult smokers and took care to avoid any product design

or marketing that would attract smokers or young adults.

In our next discussion, we'll describe the pharmacokinetic and subjective testing that supports the contention that we have been successful in producing a product with acceptable characteristics and safety.

Thank you very much.

DR. SAMET: Okay. Thank you. Don't go away. Maybe perhaps we'll see if there are questions for you.

Just one. Are these products available nationwide?

DR. WRIGHT: Yes, although they are more common in the northeast.

DR. SAMET: Other questions for Dr. Wright? Yes?

DR. BALSTER: You defined the market as adult smokers concerned about their health.

DR. WRIGHT: I made a mistake there. It's also smokeless tobacco users.

DR. BALSTER: Okay. Obviously, the

Stonewall product, would you agree, is actually targeting the chewing tobacco user, not smokers?

DR. WRIGHT: Dippers.

DR. BALSTER: And then the concern about the health part, I mean, the labeling on the package says "satisfies the tobacco need." And so when I read that statement, I'm not sure what you would associate that statement with, but I would associate that statement with basically using it to prevent withdrawal and to treat tobacco withdrawal symptoms when smoking is not possible.

Would you comment on whether or not this satisfies a tobacco need? What does that phrase mean, in your mind? And if it doesn't mean satisfying essentially a replacement for tobacco withdrawal, what is the purpose of that phrase?

DR. WRIGHT: It's a tobacco product. It delivers whatever tobacco delivers. We were specifically enjoined by applicable law from trying to promote the product as a less harmful product.

DR. BALSTER: Right.

DR. WRIGHT: Or as a way to quit smoking, so

we couldn't.

DR. BALSTER: I'm just curious by the specific phrase "the tobacco need." I just find that phrase a curious one. I mean, one thinks about needing a cigarette, I suppose, when one is experiencing withdrawal.

DR. WRIGHT: In part 3, we'll get to the studies that we did on smokers, and I can assure you, after about an hour or two without letting them have cigarettes, they need a cigarette.

DR. BALSTER: Okay.

DR. SAMET: Neal?

DR. BENOWITZ: I'm just curious about one statement in one of your slides, when you say that "we made these products because it's the right thing to do." And I'm just curious, because there is a literature that says when people can't smoke and they get frustrated and have withdrawal symptoms, a number of them quit. And one concern about having something that relieves withdrawal symptoms is they won't quit because they now have some other thing to do.

So why do you think this product is the right thing to do?

DR. WRIGHT: It depends on the nature of your approach to the American population. I think a very strong case, Neal, can be made to limit smoking and the intended risks on others. But I think attempting to force people not to use tobacco because you think it's the right thing for them to do is probably not the right thing to do.

DR. BENOWITZ: Okay.

DR. SAMET: Other questions? Yes, Bruce?

DR. SIMONS-MORTON: Just a question about the Parascandola paper. They cite a prevalence rate of 2 to 3 percent.

What is the denominator for that?

DR. WRIGHT: Stores, I believe. Let me get back up to the study that you're talking about.

DR. SAMET: That was one of the national surveys, if I recall. The paper is in the materials provided for the meeting.

DR. WRIGHT: Of those surveyed, those who had used PREPs, one of the PREPs, I believe, was 2

and a half percent.

DR. SAMET: Patricia?

DR. NEZ HENDERSON: I've opened up one of the packets, and it's actually quite easy to open.

DR. WRIGHT: Well, you're rare.

[Laughter.]

DR. WRIGHT: You wouldn't believe the --

DR. NEZ HENDERSON: I mean, I'm not -- yes.

DR. WRIGHT: I didn't say it was impossible.

[Laughter.]

DR. WRIGHT: I just said we use child-resistant packaging that came in at F2 on its seal. That's how your medications are packaged. We did not invent the packaging. We went and looked to see how over-the-counter medications were packaged, and that's the same kind of packaging that your Benadryl and other things that you buy in the drugstore are packaged.

DR. SAMET: I'm afraid that since you opened it, you're going to have to pay for it.

[Laughter.]

DR. SAMET: Yes?

DR. BALSTER: Being relatively new to this field, I've seen the tobacco-specific nitrosamine and other of those toxic products reported in various measures, like parts per billion, nanograms per gram. I've seen them in total amount per sort of unit dose.

Do you have any specific comments on what would be sort of a common nomenclature that would be the best and able to sort of allow us to compare products and to think about these things in comparison with one another?

What is the best metric for content?

DR. WRIGHT: We think parts per billion. It used to be parts per million, but then we got products that had levels that were lower than one part per million, so we went to parts per billion.

The best metric -- there are two, and we'll talk about those in a later discussion. But it's both content per unit, so you know what's in the thing you're using. And we also think it's important to give it per milligram of nicotine, for reasons that I'll talk about later.

DR. SAMET: Let's see. Mark, do you have any questions?

DR. CLANTON: I'll wait for the safety discussion.

DR. SAMET: Okay.

Thank you. Thank you, Dr. Wright.

Then we'll move on to Aaron Williams, vice president, Smokeless Product Development, R.J. Reynolds.

Dr. Williams?

Industry Presentation - Aaron Williams

DR. WILLIAMS: Good afternoon. Thanks for the invitation to R.J. Reynolds. In this first talk, we wanted to go over kind of the design, development and marketing of dissolvable tobacco products. First, I'm going to give you a little background, get into the design, and then talk about the product and the marketing of the product.

Kind of some historical background. In 2001, Brown & Williamson Tobacco and Star Scientific began a relationship looking into dissolvable tobacco, and Ariva was launched by Star

Scientific in 2001. So, as Dr. Wright said, the products have been on the market for about 10 years.

Stonewall was launched by Star in 2003, and Interval was followed by Brown & Williamson Tobacco in 2003 in Louisville. Then in 2004, there was a report by the Star Scientific Consensus Panel on low nitrosamine smokeless tobacco. Soon after that, Brown & Williamson and R.J. Reynolds merged companies. And at the end of 2004, we terminated the Star contractual agreement, which triggered a four-year non-compete, which, at the time, was called hard tobacco. So we were not able to work on dissolvables until the end of that contractual agreement. So in 2006, R.J. Reynolds launched Camel Snus, and then in January 2009, we launched Camel Orbs, followed quickly by Sticks and Strips, which did not interfere with that contractual relationship.

Before I get into the design of Orb Sticks and Strips, I want to kind of give you a little background on tobacco product development and

design. The primary objective of product development and design is to produce a marketable product which meets or exceeds the expectations of adult tobacco consumers. So you have to make something that the consumers will buy and what they want.

You start this off by -- we talked with -- and you'll see the phrase "adult tobacco consumers" and "ATC" throughout the presentation quite a bit. But we start this off, we're basically having an ideation, brainstorming session, do qualitative research, and come up with ideas in discussions with adult tobacco consumers 21 or older.

Then you develop prototypes, test different prototypes, test them internally; do they fit what you're asking for. And then, at that point, you go through quantitative research to make sure it met the objective of what you're trying to develop.

So the process, in general, is you start with a concept, ideation, refinement through qualitative research on the front end. Then you go

through the prototype development and design. So you've got to think of the technical feasibility, the sustainability; is this something that you can make; is the technology available; is it sustainable.

You make many different prototypes and improve upon each one. Then we conduct product stewardship, where we make sure what we do does not increase the inherent risk associated with tobacco. So any other additives or things that we put in there do not increase that inherent risk.

Then you do quantitative research, so consumer acceptability studies. And then once you have a product, you're ready for market, you work on specifications, develop your bill of materials, and then into production, you look at quality control and quality assurance.

Just kind of a background, basic upfront idea of the process.

So in 2007, we embarked on looking at research with adult smokers. This was not with adult tobacco consumers, but with adult smokers

aged 21 to 45, and did qualitative research around these smokeless tobacco concepts.

Snus was relatively young at this time. Not a lot of people knew about snus across the U.S. And we used a process called sequential recycling, which is a type of qualitative research, where we would talk to focus groups, and we'd present them with Ariva or with snus, and kind of show them the new age type tobacco products, and where are we going with this, and then what are the benefits, is this something that you would use, and there was a lot of excitement through that.

So then we go to another group, validate the same thing, and then we'd start talking to them about, well, what types of products would you like, what type of form, what type of size, what type of this, what type of that. And you keep diverging through this process and come up with a lot of different ideas, a lot of different things, and then you continue with different groups and ultimately start converging in. And at the end of it all, Camel Orbs, Sticks and Strips were the

outcome of this research. So these products were developed by adult smokers for adult smokers.

Some of the feedback they gave us through this process. They wanted a range of offerings. They didn't want just one type. They wanted different shapes. They wanted acceptable taste or they wouldn't buy it. They wanted complete dissolve and different dissolve times, and they wanted contemporary packaging. They liked the innovative nature of this product and they wanted the packaging to convey that innovative nature.

So some of the internal product objective designs that we put upon ourselves, one was that tobacco had to be the predominant ingredient. So tobacco is the number one ingredient in all of our products. All other ingredients had to be food, pharma grade or GRAS, which is generally recognized as safe ingredients. It had to meet GothiaTek constituent limits, and I think Dr. Garner will talk about that further in the next discussion. And it had to be adult tobacco consumer acceptable in terms of visual, oral and taste sensory. And

then cost and scalability, we wanted to make sure that this is something that we could make and scale up if it were to be a big market success.

So initial prototype development. Not a lot of us had used dissolvable tobacco before, and there are lots of different tobacco types, grades. So we started off by testing all these tobaccos. Let's put them into some wafer-type things and taste them. What do they taste like? What attributes do they provide? Are they good, are they bad? So through this big range study, we determined what's good and what's bad in terms of types of tobacco.

Then we looked at different technologies. We looked at bandcast, extrusion, pelleting technologies. So what types of technologies could we produce these forms that tobacco smokers or the adult smokers had asked for?

So through all this development, we got some key product attributes that we used to kind of judge the success of the product. So some of the key attributes that came out of this were color,

color is an important attribute; mouth feel, how does it feel when you put it in the mouth; dissolve time; irritation; bitterness. That's key. There has to be a proper -- there has to be an irritation and a bitterness associated with it to help define the tobacco, but there has to be a balance with the sweetness. So irritation, bitterness, tobacco taste, flavor, sweetness, size were all deemed important attributes in the development of the product.

Kind of a top-line processing view -- I think Dr. Wright's presentation gave a little more detail, but it's very similar. In terms of Sticks, Strips and Orbs, we all come in with the processed tobacco. In the case of Strips, we blend it with other excipients and flavor. Then we extrude it flat and dry it, and then we roll it up, kind of like paper towels. And then we take it, unroll it, and as we unroll it, we cut it and then that creates the strip that we use.

For Sticks, we do a very similar thing. We add the excipients, flavor, extrude it, dry it, cut

it to size. In this case, we extrude it in a long cylinder and then cut it as we make it.

In terms of Orbs, we blend in the tobacco excipients, we granulate it, which is very similar to the Ariva and Stonewall. Then we blend it, we add more excipients and flavors, press it, coat it, pack it. So a very simple process for all these products.

So on the market launch, we launched originally Camel Orbs in the three cities. January 2009, they launched into Portland, Oregon, Columbus, Ohio, and Indianapolis, Indiana. And six months later, we followed with Camel Sticks and Strips.

So now I want to kind of go into, from a marketing standpoint, what did we study and what did we learn, and what changes did we make, because we did recently re-launch this in two new cities.

So in terms of marketing studies that we conduct post-market introduction, we do what's called retail intercept studies. So if one of our trade marketing representatives is in the store,

they see someone purchase it, they'll go up to that person, verify that person is 21 or older and a tobacco user, and then they ask them questions in terms of demographics and other things. And I'll talk about the details on the next slide.

We do buyer studies. This is where we put a sticker on the back of packs and say please call this 800 number. We'll give you a little bit of money and we'd like to talk to you, learn about demographics, usage patterns, and other things like that.

Then we do awareness trial purchase studies. This is with our internal database of consumers, of smokers, and we'll call them up and ask them questions, are you aware of this product, have you tried it, have you purchased it.

Then we do promotion studies, and this is -- the last two are less effective. Promotion studies are effectiveness of certain promotions that we have on the different products. So this dollar off, was that appealing, was it not, did it tend to make you want to purchase the product.

Then marketing platform studies. These are studies that we do to look at dissolvables versus snus versus moist versus cigarettes and just the entire platform of tobacco.

So the types of data that we get. We get awareness trial and purchase levels. We get the demographic profile among the product triers and buyers. We get the future purchase intentions of prior triers. So we say did you try it, yes or no; was this something that you would buy again, yes or no; and, then the reasons for trying, buying or rejecting.

The product and proposition understandings, their likes, dislikes; when do you use it; how many do you use per day. And then response to and perceptions of promotional offers. And then we have the basic shipment volume, retail uptake, market share, and average selling price. So this is the type of data that we collect through our post-market studies.

Some of the learnings that we got out of the first three cities before we re-launched, the first

one was that the concept was relevant. This is something that smokers wanted, but the product and the packaging did not deliver to their expectations. The packaging was a barrier, very hard to open. A lot of people wouldn't buy it for that reason, and the products had low acceptance in terms of different attributes.

So we improved on all the products. We developed a new pack, which is a little more innovative and much easier to open, yet still child-resistant and senior-friendly. And then we moved to an all-mint platform. The purpose of this was consumer confusion initially. We had a mellow flavor and we had a mint flavor, and people were already struggling with what type of form to buy; do I buy the Orbs, do I buy the Sticks, do I buy the Strips; and, then, do I buy mellow, do I buy mint.

So in an early market, in lead markets, you really want to eliminate as much consumer confusion as possible, so we moved to an all-mint platform, which is a well known flavor among our adult

smokers. And then we offered the variety pack as a saleable unit. So there's a little bit of each product in the variety pack. So they can buy that instead of having to buy one of the other forms for an initial trial.

We learned this was a good opportunity for female smokers to switch. When you look at smokers, about half of smokers are female, and there's not really a good destination smokeless product. So if we really want to migrate smokers to smokeless, from a harm reduction perspective, female smokers don't have a good destination place.

We found in our studies that this was a very good place for females. There's high adoption among females, a little bit higher than what Star saw in their studies. So we ended up making sure that we had those consumer touch points on adult female smokers.

Retail presence must convey innovative nature category. So this is a new, innovative product, even though it has been around 10 years, in terms of the cities we were in and the presence

in those cities. So we created higher impact merchandising point of sale materials to help further differentiate the category.

Then we had the debate. Now, we've got new products and new packaging. Do we put them back into the same three cities or do we go somewhere else? And there are pros and cons to both ways. If we go into the same cities, we can learn the success of the changes that we made and did it make a difference, or if you go to a whole new city, you start from fresh, you get a whole new read and a new baseline, and that's what we decided to do. So we decided to re-launch in these cities versus expansion within the three cities we were in.

Then the traditional retail channels didn't reflect the newer, innovative category, and this was driven, again, by the female side. Females tend to buy their cigarettes more in grocery stores and in drugstores, and we were only in gas and convenience in the first market. So we wanted to put the product where the females buy their cigarettes. So we decided to put it into the

grocery stores and the drugstores where they would buy their cigarettes. So we added those in, as well.

So here are the product changes that we made. Orbs, the big feedback we had on Orbs was grittiness, didn't have good mouth feel, very gritty. So we changed the tobacco blend slightly, not a major change, and then we changed the color of the coating. They perceived it to be a little too dark. They wanted just a little bit lighter. So very similar color, but just a little bit lighter.

Sticks, we went -- again, grittiness -- went to a new tobacco blend, and it was only sold in the mellow flavor. Now that we're on this all-mint platform, we put it to the mint flavor.

Strips, we were using bandcast technology. The feedback we got is it was way too thin. They didn't like it, it dissolved too fast, too thin. So, in essence, we doubled the thickness. And that didn't fit well with that technology, so we moved to the extrusion technology, which required a new

formulation, because the excipients you use in bandcast versus extrusion are completely different. And then we optimized the packaging. So the new packs meet the CPSC guidelines, and were tested for both child resistance and senior-friendly effectiveness.

So we re-launched the products into two cities in the first quarter of this year, in Denver, Colorado and Charlotte, North Carolina. And just to give you an idea of the current product composition, these are sensory-driven, with wanting tobacco to be the predominant ingredient. You can see all three of them have approximately 30 percent tobacco makeup, with the nicotine level being 1.2 milligrams of nicotine in Orbs, 2.4 milligrams in Sticks, and 1.3 milligrams in Strips. And the pH for all the products is 7.8.

Here's a picture of all the products. You see Strips, Orbs, Sticks, and at the end is the variety pack, which has all three of them inside.

So, in conclusion, dissolvable tobacco products aren't new. They've been around for

10 years, first with Star Scientific. These products were developed by adult tobacco consumers. In essence, they were developed by adult smokers and the intended use is adult smokers. They are intended for smokers who are interested in lower risk tobacco alternatives. This is part of our goal of harm reduction and migration of trying to move smokers to lower risk tobacco alternatives. We launched the product in three cities. We learned from the three cities from our marketing studies and we re-launched into two new cities.

I think that concludes it.

DR. SAMET: Okay. Thank you.

Patricia?

DR. NEZ HENDERSON: On one of your slides, you targeted -- you were saying that you were targeting female smokers between 35 and 50.

DR. WILLIAMS: Right.

DR. NEZ HENDERSON: I just have a problem with that, actually. You're isolating -- you're not looking at the childbearing population, which is probably --

DR. WILLIAMS: We are -- what we saw, early adoption rates among those females, and it was the 35 to 50, was very strong. So that's where we wanted to go. We have Camel Snus. We have other products out there that compete with dissolvables in terms of trying to reduce risk, as well. But it is age 35 to 50, but it's not focused on 35 to 50. We want to make sure -- it's still broad. About 70 percent of dissolvable purchasers are male, 30 percent are female. But we wanted to make sure that we did hit the female 35 to 50. So it's still generically broad.

DR. NEZ HENDERSON: So in your presentation, you're making it look like this is your target population and you're excluding the childbearing female, which is 18 to 35.

DR. WILLIAMS: Right. No. It was an increased focus, but not -- we're still very broad. We want to touch all smokers with these products.

DR. NEZ HENDERSON: Okay. And then do you try these products yourself?

DR. WILLIAMS: I have, yes. I use them.

DR. NEZ HENDERSON: And you use it.

DR. WILLIAMS: Yes.

DR. SAMET: Neal?

DR. BENOWITZ: I've got two areas of questions. The first is about the product itself. One is we heard from Star Tobacco how their manufacturing process assesses nitrosamine content and how they choose their tobacco. So I'm curious to know how you control it. And then the second is 30 percent of the product is tobacco, and what's the other 70 percent?

So those are the two questions about the product constituent.

DR. WILLIAMS: Sure. In terms of the tobacco, we do pre-select tobacco that meets the GothiaTek constituent limits, and I think Dr. Garner will talk a little bit about that further in our second talk. But we do select based on that. So there are limits in terms of TSNAs, heavy metals, BaP. And that's how we -- we want to meet those constituent limits.

In terms of what the other 70 percent are, I

mean, they are basic excipients. They're fillers, they're binders, things to make a pellet in order to crush it and hold it and have it hold in a store and maintain through shipping. It's just generic binders, fillers, and other excipients that many companies use.

DR. BENOWITZ: It would probably be good for our committee, at some point in time, to know what they are, because that will be part of our consideration.

DR. WILLIAMS: Okay.

DR. BENOWITZ: And the second general area has to do with sort of the marketing and the reasons why the people use it. So when you do focus groups, people who choose to use this, why are they choosing to use it?

DR. WILLIAMS: They're choosing to use it for -- I mean, a lot of the feedback we get are I'm tired of going down 17 flights of stairs to go smoke a cigarette. I'd like to sit in my office and get the tobacco satisfaction in there. So a lot of it is about times when you can't smoke or

times when it takes time and effort to go outside. When it's 50 degrees below zero, this is alternative for them.

DR. BENOWITZ: It makes sense. But then how do you advertise it? You didn't show us any of your advertisements. How do you market it?

DR. WILLIAMS: No. We market this as we tell people to switch. Our ultimate goal is we want to be able to provide the harm reduction story and tell them to migrate, but we can't do that. By law, we're not allowed to do that. So we tell them to switch. I would love to be able to give them that harm reduction story so that they can make an informed choice and know about the risks associated with this product versus others, versus smoking.

DR. BENOWITZ: Thanks.

DR. SAMET: I think just to maybe follow-up on Neal's question, I was struck by the wording that you used and then reiterated on the conclusions. You actually said "developed by adult tobacco consumers for adult tobacco consumers."

DR. WILLIAMS: Right.

DR. SAMET: Let me just ask you to go a little further. And I understand you used the focus group technique to assess need for alternatives to smoke tobacco, if I understand what you described --

DR. WILLIAMS: Right.

DR. SAMET: -- this iterative process. But did that process itself lead to this array of products or did it lead to -- I think Neal was alluding to a search for a desire to have some alternatives. In other words, how did you go -- at least as you laid it out, you went from some focus group process to Strips, Orbs and Sticks.

DR. WILLIAMS: I can give you a little more detail there. They found a need and a benefit of having this type of dissolvable product, and then we had to ideate around different forms and types. And we actually got well over a hundred different ideas, and Sticks was one, Strips was one, Orbs was one.

So they gave us lots of ideas, some of them very eccentric, some of them that you just can't

make. And we further refined it with those consumers to narrow down, to ultimately they said they wanted something that was stick-like, that lasted around 20 minutes, that took a while to dissolve, that was something that would stick out of my mouth, so a little more extroverted, something I could use to show off to people. Others said they want something discreet like a strip that they could put in their mouth, get quick satisfaction, dissolved in a couple minutes. And then others liked the Orb and Ariva idea.

So, ultimately, it call came down to those three products.

DR. SAMET: Bruce?

DR. SIMONS-MORTON: I was just curious, in your research, if you learned how non-tobacco users or occasional chippers react to this product and is the kind of product that they're likely to adopt?

DR. WILLIAMS: We do not do any research with non-tobacco users. So if you say you don't use tobacco, we don't talk to you. And we have to verify that you are a tobacco user and that you are

21 years old. So those are the only people that we talk to.

DR. SIMONS-MORTON: There are those who use tobacco on occasion, but are not regular users. Are they included in your research?

DR. WILLIAMS: We ask them what is their -- are you a tobacco user, yes or no; what is your predominant form of tobacco use, is it cigarettes, cigars, smokeless, other things; and, we get that type of information. We do get some information in terms of, yes, I use 10 cigarettes per day or I use 30 cigarettes per day. And I haven't seen the breakdown in terms of number of cigarettes per day versus how many of these they use per day. We do have that data, can provide that data to the FDA.

DR. SAMET: Karen?

MS. DELEEUW: Do you have any of the results from the re-launch yet?

DR. WILLIAMS: Not yet. We're relatively early. We just got good distribution into all the channels that we wanted. The early read, I mean,

the product is selling well. We are doing quite well, in fact, but it's very early on and it's hard to tell how successful it is. Typically, you need to give it about nine months before you get a good read.

DR. SAMET: Let me see. Patricia, did you have another?

DR. NEZ HENDERSON: Yes. Following up with the question about non-tobacco users, I'm female and I'm actually kind of interested in this, because it doesn't -- it's not like it's a full cigarette, and I'm thinking maybe I should cut it in half and try it and see how it feels.

So I guess that's the part that I'm interested in is the non-tobacco user, those that have never smoked in their lives and now this product comes out. I'm thinking it's probably a little bit safer. If I'm a general person just out there looking at products, I would think that it would be a little bit safer than a tobacco product or a cigarette product.

DR. WILLIAMS: I'm not sure your assumption

is correct. I think in the third presentation today, you'll see that might not be true.

DR. NEZ HENDERSON: Well, this is from my experience.

DR. WILLIAMS: Sure.

DR. SAMET: Arnold?

MR. HAMM: Yes. Just out of curiosity, what's the retail price, say, in North Carolina, because that's one of your two test markets on that?

DR. WILLIAMS: Right. The retail -- the easier way of stating it is we target our retail price to be below a pack of cigarettes.

MR. HAMM: Okay. What's the tax structure?

DR. WILLIAMS: This is taxed as a smokeless tobacco product.

MR. HAMM: Okay.

DR. SAMET: Let's see. Robert?

DR. BALSTER: I haven't actually seen the product at any time. I don't know if you have any in the trunk and you could bring some tomorrow. But could you describe for me how the child

protection thing works from that? I've seen a picture of the Orb, where it looks like the pills just tumble out of a box.

DR. WILLIAMS: Dr. Ogden has some samples here.

[Laughter.]

DR. WILLIAMS: Well timed. We actually spent a lot of research and time on this package design. And to make it child-resistant, there's a button on the top and bottom that you have to press at the same time and then you open it up. And the dexterity of reaching across is something that children have a hard time doing and pressing both at the same time. So it's been successful for other product types. We did have this tested by fully certified CPSC testing. It did pass child resistance and senior-friendly effectiveness.

DR. BALSTER: Once it's then opened up, then there's a certain number of pills or there's a certain number of sticks. There wouldn't be much limit on how many of those pills or sticks you could take.

DR. WILLIAMS: That's right.

DR. BALSTER: I mean, they're not individually blistered, right?

DR. WILLIAMS: They're not individually blistered.

DR. BALSTER: So it's just a question of getting into the reservoir. Once you've gotten in --

DR. WILLIAMS: Correct. Similar to prescription drugs and other things that are sold in bigger packs.

DR. BALSTER: I understand.

DR. WILLIAMS: According to the -- the CPSC guidelines dictate whether it should be single-serve or you can go multi-serve, and these, they went through the multi-serve.

DR. BALSTER: And do they automatically close? If someone opened it and they just took out one unit dose, does that sort of automatically close or what --

DR. WILLIAMS: No.

DR. BALSTER: So if someone has a pack --

DR. WILLIAMS: If you open it up, it's open. You have to close it again.

DR. BALSTER: I see. So if a parent has it opened on their coffee room table or whatever and then they don't close it, it sits there as several pills.

DR. WILLIAMS: Sure. And I would hope the responsible parent wouldn't leave them --

DR. BALSTER: I understand.

DR. SAMET: John, did you have a --

DR. LAUTERBACH: No, I don't.

DR. SAMET: You don't? Okay.

Mirjana?

DR. DJORDJEVIC: I just wanted to ask you the question, do you have the values for free nicotine? Because you measured pH, you measured nicotine. Do you have the values for free, unprotonated nicotine?

DR. WILLIAMS: It's 7.8 pH. It's about 38 percent free nicotine.

DR. DJORDJEVIC: And, also, do you have information whether Sticks are preferred products

compared to Orbs and Strips because they have a higher nicotine level?

DR. WILLIAMS: Our early read in the market right now is the variety pack is selling the best, because people are unfamiliar with this, so they want to buy something that has all three. And then Sticks, Strips and Orbs are all about the same in terms of sales. So all three of them are about the same in sales, with variety pack being much higher.

DR. DJORDJEVIC: Thank you.

DR. SAMET: Let's see. Who else? David?

DR. ASHLEY: There were just two terms that you used. I just wanted to make sure I understood exactly what they meant.

DR. WILLIAMS: Sure.

DR. ASHLEY: On slide 9, you were talking about product attributes that people had brought up to you. And you had the term "mouth feel."

DR. WILLIAMS: Right.

DR. ASHLEY: And I just wanted to see if you would explain "mouth feel."

DR. WILLIAMS: Mouth feel -- and this was

the good example of why we had to redesign Orbs. It has to be something that sits comfortably between your cheek and gum. And if you have grittiness or it's lumpy, there are different ways that consumers will get irritated. Now, if they want to put an Orb in their mouth, they want it to sit there and not necessarily have to feel grittiness, sandiness, that type of mouth feel -- and it has to sit in there comfortably, so it's not like a triangle that's poking your gum or your lip.

DR. ASHLEY: And there was a second term, and it was on slide 16. Again, I just didn't know what you meant when you said -- down under Strips, it says "which required a new formulation."

DR. WILLIAMS: That's correct.

DR. ASHLEY: And I didn't know whether that meant the design of the product or the manufacturing steps, what you meant by "formulation."

DR. WILLIAMS: It required different excipients. When you move from

bandcast -- bandcast is a very wet method, with a lot of water that you put over a band and then dry. Extrusion is much less water involved. And you have different types and ratios of excipients that you use, again, that's very common, that are all food/pharma grade.

DR. ASHLEY: So it really was the things that went into it, I'm sure. In addition to the fact that you were doing extrusion instead of bandcast, it actually was the things that went into it.

DR. WILLIAMS: Right.

DR. SAMET: Let me see who else has questions. John?

DR. LAUTERBACH: Dr. Samet, can we -- this is not a question, but I think sooner or later on this committee we're going to have to discuss the CDC calculation of free nicotine versus what free nicotine is in a product and some of these other things. And I can pass you later on a publication that you might want to look at.

DR. SAMET: Thank you.

Neal?

DR. BENOWITZ: I just have a quick question about where you advertise or where you're planning to advertise. We heard from Star that they're doing just sort of point of purchase.

DR. WILLIAMS: Right.

DR. BENOWITZ: Where are you planning to advertise, what sort of venues?

DR. WILLIAMS: We advertise -- we have point of sale. If you walk into a store, you'll see it on the walls, you'll see it behind the counter with the cigarettes.

DR. BENOWITZ: Besides that.

DR. WILLIAMS: We also -- we send out direct mail to our smoker database. So we'll send them a card in the mail if they live in that vicinity in Charlotte or Denver, send it to them and make sure that they are aware of the product.

As part of the retail intercept, if we see a consumer buying a pack of cigarettes where Orbs, Sticks, Strips are sold, the trade marketing person could go up to that person, again, verify age,

tobacco user, and then tell them about the products.

DR. BENOWITZ: How about in the press?

DR. WILLIAMS: We do press. We do magazines. I'm not sure of the details, but you have -- the magazines have to have a certain age of viewership that they're advertised in. So it will be -- we don't put it in every magazine. There has to be a certain percent age viewership protocol that goes with it, as well.

DR. SAMET: So since everyone is playing with these, is there any dermal absorption?

DR. WILLIAMS: Any what?

DR. SAMET: Dermal absorption.

[Laughter.]

DR. SAMET: Or does it have to be wet?

DR. WILLIAMS: It depends on how thick your skin is.

DR. SAMET: I'm vaguely serious.

DR. WILLIAMS: I don't know. I think it would depend on --

DR. NEZ-HENDERSON: I have a question. On

the back of this package, it says 75 percent of this tobacco is from the U.S., the other 25 percent is from foreign tobacco.

DR. WILLIAMS: That's correct.

DR. NEZ HENDERSON: Can you tell me a little bit more about that, as well as if you're using different blends of tobacco, how do you determine that this one stick is 2.4 milligrams of nicotine?

DR. WILLIAMS: We use the same blend of tobacco in all three products. The details, the offshore or onshore, we have provided to the FDA. But in an open forum, I don't want to divulge that sensitive information.

But it's normal tobaccos that are found commonly in cigarettes with normal nicotine levels that you see. The reason the stick is higher nicotine is because it's about twice the weight as an Orb. So 225 milligrams for an Orb, about 450 milligrams for a stick, same tobacco, roughly same percentage. So that are the differences there.

DR. NEZ HENDERSON: And just a follow-up question. How do you use the stick?

DR. WILLIAMS: A lot of people use it different ways. Some will keep it in their mouth and just hold it there like a toothpick. Some people break it and put it in between their cheek and gum. Some people break it and give some to other people. It's something that each individual user can create new rituals with in how they want to use it.

DR. SAMET: Okay. Thank you. I think, obviously, your presentation generated a lot of interest.

Why don't we take a break for 10 minutes, until quarter of 3:00? Thank you.

(Whereupon, a recess was taken.)

DR. SAMET: If everyone could take their seats, please, we'll go ahead and get started. We're going to move on to the presentations on abuse liability, and health risks.

Our first presenter is Dr. Charles Garner from R.J. Reynolds Tobacco Company.

Industry Presentation - Charles Garner

DR. GARNER: First off, thanks for the

invitation to speak to you guys today. The title of my presentation is "Dissolvable Tobacco Products: Chemistry and Toxicology."

What I want to do, first off, just the objectives of the presentation, is to go over our stewardship principles and the process we use for the evaluation of smokeless tobacco products, and then go into a bit of detail about the evaluation we did to support the dissolvable tobacco products, Sticks, Strips and Orbs.

It's going to go kind of like this. I'm going to start with the stewardship principles, and then I'm going to go through the stewardship approach that we used, starting with the ingredient assessment, chemistry of the products, the in vitro studies we conducted, and the in vivo studies, and then I'm going to talk in a little bit more detail about the child-resistant packaging.

So starting with guiding principles. The primary objective of the product stewardship program at R.J. Reynolds Tobacco is to ensure that product changes that we make do not increase the

biological activity of our products. Stated a little bit differently, we ensure that nothing we do or add to our products will increase the inherent risks associated with these products. There are risks with tobacco products. That risk can be different from different categories of products. But whenever we make changes, we want to make sure that we don't increase that risk.

So some examples of product stewardship changes would be, say, we're going to use a material that was not previously used or we're going to use a material at a higher level than was previously used; any changes or modifications to our manufacturing processes. And most relevant for this particular talk are what we call non-traditional products for Reynolds.

As you heard in the earlier slides, the dissolvable tobacco products have been in the market in the U.S. since 2001. We put them out in 2009. So they're relatively new for us. So we did product stewardship work on these particular products.

The product stewardship was actually grounded in Reynolds for a number of years. We've been doing this for 20-plus years to evaluate our cigarette products. And most recently, this concept has been extended to smokeless products, starting with snus, which was our first smokeless offering. And the corresponding FDA terminology for the concept of product stewardship at R.J. Reynolds is substantial equivalence.

Now, the foundation of the product stewardship program is based on what we call a tier testing strategy. And what that means is that the degree of work that is done to evaluate changes or new products is based on the likelihood that that modification might increase the risk. So if it's a small modification in a flavor, that likelihood is probably relatively low in comparison to a brand new product or a significant change in a manufacturing process.

What forms the basis of this is a review by board-certified toxicologists and the determination of what we call a level of concern. So level of

concern can be 1, that's the low level of concern, or it could be level of concern 5, based on the degree of the changes and modifications. And any level of concern that's greater than 1 will require chemical testing and/or biological testing.

So I'm going to start with the ingredient assessment. The ingredients that are added to tobacco, in this particular case, added to our dissolvable tobaccos, are evaluated to determine whether that ingredient might pose a health risk. And it's evaluated by looking at two things, the potential hazard of the ingredient and the level of exposure to the consumer of that ingredient in question.

Now, some of the things that we look at when we're considering ingredient usage is, is it something that we currently use at an appropriate level already; is it something that's considered a food or a food product, either by the FDA or by the USDA; has it been granted the GRAS status, which is generally recognized as safe by FDA or by another expert panel; and, what information is available in

the literature to support the use of that ingredient in the particular product at the intended use level.

So after we reviewed all the ingredients that are used in Sticks, Strips and Orbs, all the materials that are used are either food grade or pharmaceutical grade, except for the tobacco. So that was a pretty straightforward assessment.

The second thing I'm going to talk about is the chemistry evaluation. And chemistry evaluation is one of the tests that we use, but it's a very important test, because it allows us to compare the dissolvable products to a broad range of smokeless product in the market, and you can look at levels of toxicants in dissolvable tobacco products across that broad range.

As Dr. Williams pointed out in his presentation, one of the targets that we had in the development of Sticks, Strips and Orbs, we wanted it to hit the GothiaTek standards. Now, I don't know how much you know about GothiaTek standards, but the GothiaTek standards is a quality standard

that was developed by Swedish Match. The chemical pieces are one component of it. There's a number of others. But they have listed some chemicals that have had the potential to cause harm.

We have nitrate, a combination of TSNAs, NDMA, BaP, and then some metals, cadmium, lead, nickel, chromium, and arsenic. And I've listed them in two different categories. The middle one, the limit with the asterisk, that's in Swedish Snus, where the moisture is 50 percent. And making comparisons sort of across a range of smokeless tobacco products, we converted that to a dry weight basis.

Now, this is the current list that we're using at R.J. Reynolds. It's basically a GothiaTek, with some added compounds. We've added some TSNAs. BaP was the only PAH that was on the GothiaTek list. We've added some others. And we've also added acrylamide. And this is based on a risk assessment we did from some market survey data.

I'm going to apologize for this slide

upfront. It is a little bit busy, but it does have a lot of information. The column to the left is product type and the number of products that were evaluated in that product type. So starting from the top, MS is moist snuff, snus is snus, LL is loose-leaf, DS is dry snuff, plug and twist are plug and twist, DS are dissolvable tobacco products, and DS-C are the Camel dissolvable tobacco products.

If you look at the list, there are a couple things you want to point out. I mentioned the moisture earlier, but there's a huge difference in moisture for these products. If you look at moist snuff, it's over 50 percent. If you look at dry snuff and if you look at the dissolvables, it's less than 10 percent. So moisture probably plays a pretty key role on how you look at these from a chemistry perspective.

But if you look at these from left to right, if you look at the TSNAs, you look at the PAHs, and you look at some metals, you see that, on the bottom, the dissolvable tobacco products are quite

solidly at the low end of those ranges.

So the conclusion from the chemistry is that, clearly, the chemical constituents fall well within the market range for a broad number of categories of smokeless tobacco products, and in most cases, the chemical constituents in the dissolvables will represent the lower range for dissolvable tobacco products.

Next, I'm going to move to the in vitro evaluation that we did for Sticks, Strips and Orbs. There is no consensus as to what should constitute in vitro evaluation. But we continue to investigate the appropriate in vitro testing methodologies, as well as the extraction methodologies for smokeless products.

Now, the products that we tested were compared to basically four positive controls. We used the 2S3, which is a reference to moist snuff product, which is analogous to 1R4F or 2R4F, which I'm sure you're very, very well familiar with. We also looked at a snus product, which was Camel Snus Frost. We looked at another dissolvable tobacco

product, which was Ariva wintergreen. And we looked at Copenhagen long cut, which is a type of moist snuff.

The way we did our comparisons was we normalized on a dry weight basis, and there are a number of reasons for this. It is a suitable metric for making a comparison sort of across many different categories. The other thing is the use patterns of consumers will vary quite widely. We don't know how much people use of, say, a plug or a twist or moist snuff.

Probably most importantly, or at least second most importantly, in many of these, it's not a standardized package. Snus comes in a pack, Orb comes as an Orb, but moist snuff comes in a tin, and there is no kind of unit use for that. So it's very difficult to kind of put it on a per unit basis if there is not a unit basis to put it on.

The other thing that I pointed out in my chemistry slide is there is a fairly broad range of moistures for these products. So looking at it on a dry weight basis is probably the best way to sort

of normalize and take moisture out of the equation. And this is a method that has been done for a long time, and there's a lot of data out there in the literature looking at it on a dry weight basis. And these were some of the conclusions of the WHO study group on tobacco product regulation.

So in the Ames test, it's a pretty straightforward story. We did it plus S9, minus S9 in five strains, and the responses were weak or negative. They were totally negative in some levels of the strains. But at the end of the day, the bottom line is they were well within the range of those smokeless products that were tested. In most cases, they didn't have a lot of activity at all.

We also looked at the micronucleus assay, which is a genotoxicity assay. It's specifically a clastogenicity assay, and we saw the same results. They were equivalent to or statistically less genotoxic than other smokeless products.

The neutral red assay is a cytotoxicity assay, and the results for that were essentially

the same. They were equivalent to the controls tested or less cytotoxic than some of the controls tested.

So to sort of summarize that, the three Camel smokeless products were equivalent or less active than other smokeless products in that battery of in vitro tests that we used.

Moving on to the in vivo evaluation. And I'm not speaking on behalf of Star, but I'm going to pull something that came out of Star. In 2003, Star was able to provide an unrestricted grant to fund the creation of an expert consensus panel to answer the question about relative risk of smokeless tobacco products. And the committee made a number of recommendations as to work that needed to be done to characterize the risk, but they did not recommend animal testing to address any of the concerns.

But there are studies in the literature, feeding studies, where animals are fed, as part of their diet, some tobacco. And the first one I'm going to point out is a Homburger study which was

done in 1976.

Now, this is a quite interesting study. It looks at the initiation and promotion. So it's a carc study and a co-carc study, and it uses two PAH strains of hamsters that are sensitive to pH. The diet was matched. The control diet had 20 percent methylcellulose as kind of a fiber control for the tobacco, and then they had 20 percent snuff, which was powdered tobacco, in the treatments. And then the animals were pretreated with the carcinogen 2-methylcholanthrene at two different doses, 5 and .5 milligrams.

The results of this study did not show either any carcinogenic changes or any co-carcinogenic changes after the ingestion of tobacco. The levels of cotinine in the serum, as well as the food consumption and body weights, showed that there was an adequate intake of tobacco in the experimental animals. And tumors in the MC-treated animals showed that the strain that was used for this study was an appropriate strain.

The conclusion of the authors was that the

administration of 20 percent tobacco in the diet did not induce either a carcinogenic change or a co-carcinogenic change in these animals at the end of the study.

There was another study that was done by Brown & Williamson. When Dr. Williams gave his presentation, he mentioned an option product. Option was a product that was looked at, at Brown & Williamson, and this was a slightly different take on the study.

While the Homburger study looked at the impact of ingestion of tobacco, this was more what I would call a product study, because the first group was a normal diet control, the second one was a nicotine control that was matched for the nicotine in the test diets, the third was a tobacco pellet prototype which contained the tobacco and the ingredients, and then the third was the non-tobacco ingredients. So you could look at the impact of the product itself, you could look at the impact of the ingredients, and, then, as well as the nicotine.

The major finding from the study was a dose-dependent reduction in body weight in both the tobacco test group, as well as the nicotine group, which has been seen in animal feeding studies before with tobacco. And then food consumption tied with the decrease in body weight, and there was no change seen in organ systems. The decreases in organ weights correlated with a decrease in body weight. But there were no gross changes or any histopathological changes that could be attributed to the control, the test, or the reference articles.

So when we decided to go down the path of dissolvable tobacco products, we decided that we wanted to conduct some feeding studies. And this was a little bit different take than the other two. What we wanted to do was we wanted to compare whether the ingestion of whole tobacco, which would be in a dissolvable tobacco products, was any different from the ingestion of a tobacco extract, which would be similar to what people are exposed to when they use snus. And I think if you followed

the epidemiology in Sweden for snus, it's a pretty good story. So we wanted to have something to link the results from an animal feeding study to the epidemiology.

We started in 2008, and we ran a number of different studies, starting out with a palatability study basically to make sure that the animals would eat the diet. And then we had kind of two range-finding studies, one was a 28-day and one was a 90-day. And then started with the two-year chronic study. The first three were done in rats and mice. In the chronic study, we decided to use the Wistar Han strain of rats.

So there are a number of endpoints that we're going to look at on this. Again, this was to look at whole tobacco ingestion versus extract. There was an interim sacrifice that was done at 12 months, and I'm going to get into that in the next slide. But some of the data that was collected are concentrations of nicotine and cotinine, some observations from the clinic, organ and body weights, food consumption, clinical

pathology, and, of course, finally, the histopath.

The results from the one-year study were actually quite good. The food consumption body weight was very similar to the B&W study. The blend was equal to the extract, which was equal to the nicotine control. They were less than the control, but that is not an unexpected finding.

Spontaneous lesions, the non-neoplastic lesions, the incidence was very low. The severity score was very low, and they're very typical of the historical findings that are seen in this strain.

The neoplastic lesions were within the two-year norm. But the most important thing was we didn't see anything that was dose-related or treatment-related. So when we looked at a tobacco versus a control or an extract versus control, we didn't see any difference. And when we looked at increasing levels in either the tobacco or the extract, we didn't see any changes within increasing dose.

Then the last thing I'm going to talk about is child-resistant packaging. As Dr. Williams told

you, we decided to employ child-resistant packaging for these products. I'm kind of curious as to were they easy to open when we passed them around. I know there were some comments that was the Star was a little bit too easy. Comments we got from our consumers is they're not that easy.

There are case studies in the literature about in children who will consume a tobacco product. It could be whole cigarettes, it could be moist snuff, or it could be NRTs. And given the fact that there isn't a lot of information in the poison control literature on these products, we decided to employ child-resistant packaging.

So we put the child-resistant packaging as a requirement for these products and it has been instituted for all the dissolvable tobacco products, and it's tested by a third party, where we follow the CPSC testing guidelines.

We also registered with a company called POISINDEX, which is essentially you list all your product information, contact information, and they have it on file in case there is a report in an ER

from a child or anyone, I guess, for that matter, that has ingested these.

To date, we have not received any calls from poison control stating that a person has become ill from ingesting these products. The thing I probably need to point out is we also have an 800 number on the pack. We have a website address on the pack where you can check in to do a report, and I think there also is a "keep out of the reach of children" note on the package, as well.

I think that's all I have, and I'd be happy to answer questions.

DR. SAMET: Good. Thank you.

Questions? Neal?

DR. BENOWITZ: In talking about the health effects, you didn't say anything about oral pathology. I'm kind of curious, Star products said that they used non-cariogenic sugars.

What kind of sugars are in your products?

DR. GARNER: I believe our sugars would be characterized as non-cariogenic, as well.

DR. BENOWITZ: So essentially the same.

DR. GARNER: Yes.

DR. BENOWITZ: The second question that I have is that for the Swedish Snus, one cancer that's been of concern is pancreatic cancer. And I'm just curious if your animal models would be sensitive to nitrosamine-related pancreatic cancers.

DR. GARNER: That's one of the things that we've been looking at, and we didn't see any change in the pancreas in the one-year study.

DR. BENOWITZ: But I'm just wondering, in the animal models, if you were to feed them nitrosamines, would you see pancreatic cancer or is there a model that's sensitive to that?

DR. GARNER: I don't know if there's an animal model that is specifically sensitive to pancreatic cancer. This is the animal model that's recommended by the NTP as the most general model.

Certainly, the issue of pancreatic cancer is one that we watch. There are a couple of reports in the literature, but there's also a number of others that they do not see any difference. So

it's a good point.

DR. SAMET: Bruce?

DR. SIMONS-MORTON: One of the articles we got with the materials for this was on circulation, and it made a point about the risk of heart attacks to these.

Is that something you can study at all with these kinds of methods?

DR. GARNER: The risk of heart attacks to a dissolvable tobacco products?

DR. SIMONS-MORTON: Yes. Well, snus, I think they were --

DR. SAMET: I think you're referring to the AHA statement on smokeless tobacco.

DR. SIMONS-MORTON: That's right.

DR. GARNER: Well, I think I'm going to leave that one to Dr. Curtin, but I think when you look at the risk of heart attack, there is some information in the epidemiological literature. But, certainly, these products would fall within the general category. And based on the chemistry, I certainly would not expect them to be any worse.

If anything, the chemistry might point to them as being a little bit better.

DR. SAMET: Bob?

DR. BALSTER: So I'm having just a little bit of trouble understanding what we're supposed to take from your in vitro and animal in vivo safety data. I can certainly understand why you would do those studies. I think it's good that you did. But as I understand it, from what you were saying -- and maybe I'm just not quick enough to figure this out. But it sounded like you were actually doing those studies with sort of large amounts of tobacco itself and, in effect, not finding -- not getting negative effects in the tests using basically tobacco.

Wasn't that what you were showing us, data from tests of tobacco?

DR. GARNER: Yes.

DR. BALSTER: Not the extract, but tobacco. So you were essentially getting negative results for most everything that you tested.

DR. GARNER: Are you talking about the

in vitro studies?

DR. BALSTER: Well, both, I thought.

DR. GARNER: Well, the in vitro studies were actually an extract of tobacco.

DR. BALSTER: Okay.

DR. GARNER: Okay. So it wouldn't be a test of whole tobacco.

DR. BALSTER: I guess where I -- let me just get to where I'm sort of going with this. In trying to assess the safety of something, generally, in my way of thinking about it, you would usually have like a positive control that would reliably produce the result to demonstrate that the model is actually sensitive and able to pick it up.

I'm not really seeing where the positive control is in here, assuming that tobacco, in the way in which it's consumed in cigarettes, which we know is associated with health effects -- where is the positive control? How do we know that these models are sensitive to pick up the kind of harm that's produced by tobacco?

DR. GARNER: Well, I think, as I said before -- which model are you talking about in specific? The feeding studies?

DR. BALSTER: The feeding studies is probably where I would -- we can start there.

DR. GARNER: I think in some cases, if you know the endpoint that you're looking for, then you can choose a model. In this particular case, we don't know what specific endpoint we're looking for, so we chose a strain of rats that is used by the NTP sort of as a general screen for any kind of toxic endpoint.

DR. BALSTER: Just a clarification. So using that sort of general tox screen, which I'm generally familiar with, would testing tobacco yield signs of its toxicity? Is that sensitive to showing in animals the toxicity as now we know is associated with tobacco?

DR. GARNER: If there were a positive control that we could use, we obviously would have rolled one into it. But this is very similar to, say, if you were testing a new food additive and

you don't know what the toxic endpoint is. So you can't pick a positive control if you don't know what the endpoint is.

DR. BALSTER: That's sort of where I was seeing that, and I appreciate why you did it and I'm not questioning that. I'm just sort of saying that it isn't really informative to us so much about the relative safety of any of these dissolvable products relative to smoking or tobacco.

DR. GARNER: Well, I think as you'll see in some of the later presentations, I think you'll get quite a bit of information about the comparison of use of smokeless tobacco products to smoking.

DR. SAMET: I think just maybe in follow-up, for years, I've gone to meetings where people say, "I'm no epidemiologist, but," and then ask a question. So, now, I'll say I'm not toxicologist, but. And, actually, the question, I think, just follows up.

If we are concerned about particularly effects at the site of delivery, whether that's

increased risk of various oral diseases, pre-malignancy and so on -- in a sense, you haven't shown us an animal model that would reflect those outcomes. And perhaps none exist, which I'd like to hear from you if such exists. And then in the short-term assays -- you've shown us a relatively conventional set of short-term assays that, and in a sense you're telling us you're not sure exactly what you're learning from them.

So I think this really follows up on the question of will it be possible to have more targeted and directed testing strategies that may be informative on the effects, at last a priori, we'd be most concerned about.

DR. GARNER: I think that's actually what we're doing, is we're trying to figure out what models are the best to assess these products.

When you're talking about oral specifically, again, for smokeless products, there is a lot of epi data out there. And I'm not an epidemiologist either, but there is a lot of epidemiological data out there on relative risk of, say, oral cancer in

comparison to smoking.

The thing with these is, I mean, when you think about a moist snuff product and you put a big plug in your cheek and leave it there for however long, these products, the residence time in the mouth is much shorter than for, say, some types of traditional smokeless products.

So from that respect, I think the oral tox issues are fairly clear in the literature. We were concerned more about how does this compare to snus as far as total body toxicity.

DR. SAMET: Right. And I think right now you really don't have an anchoring point for comparing one risk to another. I recognize that there's an epidemiological literature extending backwards quite some time dealing with a variety of products, but you still don't have a point, let's say, to move from an animal assay, should you have one, to the human data. And I think even on the product comparison issue, which you alluded to, again, I'm not sure how you would line up some intermediate outcome for two products and look at

risk.

DR. GARNER: Well, again, that's why we used the extract versus the total tobacco in the animal model.

DR. SAMET: John?

DR. LAUTERBACH: Dr. Garner, have you had a report of any leukoplakia from your consumers of these products, typical solicitor persuasion?

DR. GARNER: No, we have not.

DR. SAMET: Mark, do you have any questions?

DR. CLANTON: Yes, I do. I actually tried to get in with one a couple of times on the previous session, so hopefully you can hear me.

My question goes to, I guess, the experiments with mouse being fed tobacco products or tobacco. It is possible -- really, there's two means to measure mouse blood pressure and to measure it as sort of a continuous variable over time.

I'm just curious. Was blood pressure a variable that was evaluated or measured in that mouse testing you talked about?

DR. SAMET: Dr. Garner had a hard time hearing, but I'm going to -- I think the question was were you able to measure blood pressure in the mice, and Mark thought that there were techniques to do so.

DR. GARNER: I don't have the answer to that question. I'm not sure if we measured it. I know we have provided all of the information, at least up to the one-year time point, to the FDA. But as I stand here today, I can't recall whether we measured blood pressure or not.

DR. SAMET: Thanks. Let's see.

Mark, did you have another question?

DR. CLANTON: No.

DR. SAMET: Okay. Any other questions for Dr. Garner?

[No response.]

DR. SAMET: Okay. Thank you.

DR. GARNER: Thank you.

DR. SAMET: Okay. I guess then we're going to go back to Dr. Wright from Star Scientific.

Industry Presentation - Curtis Wright

DR. WRIGHT: First, I'd like to add something to my previous talk. One of the targets for our products was to make something that women would use, and I gave you the aggregate data for male and female combined and for Ariva and Stonewall combined.

For Ariva, which is the smoker's product, we're 52 percent female, 48 percent male in terms of our usage.

Okay. Just a brief review. Our dissolvable product dissolved to powdered tobacco, binders, sugars, pH buffers, and flavors. Our design goals, our design was to appeal to middle-aged long-term smokers, reduce known carcinogens to a minimum, control nicotine dose and pH for mouth safety -- and I will get to mouth safety -- design for low abuse liability, minimize risk of adolescent use, and control or eliminate the pediatric poisoning risk.

We believe that the components that are most in need of control are TSNAs and polycyclic aromatics. WHO agrees. The recent World Health

Organization study group on tobacco product regulation stated very clearly, "Although it has not been proven that taking these things out of tobacco products will reduce human risk, there is no rationale for leaving them in, as they are known human carcinogens."

Companies have started doing that. This is the levels for TSNAs and benzo(a)pyrene for Swedish Snus. And what you see is that starting in about 1992, they really got those levels down, as they did for benzo(a)pyrene. This has some consequences, because most of the epidemiology studies that are done on Swedish Snus that are in the literature are talking about products that had 10 or 20 times the toxin load of the current products.

Even so, the result for Sweden, which I believe you are probably familiar with, has been felicitous. Sweden had an increase in snus use and a decrease in smoking. The smoking rate for males, the blue line, went down precipitously. Women in Sweden still do not use snus as much as men, and

their smoking rates have continued to climb. And as a result, the lung cancer rates in Sweden peaked and are declining for men and are continuing to rise for women.

This committee impaneled a subcommittee to come forward with what the harmful or potentially harmful constituents of smokeless tobacco might be, and they came up with a list of 40 draft choices. That list has not been finalized, but we analyzed the product for them anyway.

I will, if you like, read every line of this slide to you or you could look at it in the one that's in front of you. Same thing here, same thing here.

What you'll see is that the constituents in Star's products are lower or non-detectable as relative to other tobacco products, except for the things that we know should be there, which are the tobacco alkaloids, nicotine, nornicotine, anatabine, and anabasine.

Pharmacokinetic studies of the Star products have been done. As you can see, this was a

comparison done by Kotlyar looking at Commit, Copenhagen, Stonewall and Ariva. Copenhagen delivered quite a bit of nicotine. Stonewall delivered about the same as Commit, although a little slower, and Ariva was about half to a third of Stonewall.

Cobb did a single-session study of the pharmacokinetics and subjective effects of Ariva, Commit, Quest, and the individual's own brand cigarettes, which were full flavor 1.1 milligram cigarettes. These were people who had been abstinent overnight. Cigarettes delivered the most nicotine. The prep products delivered less. And, overwhelmingly, in terms of relief of withdrawal symptoms or tobacco effect or liking, cigarettes outperformed any of these products handily.

Blank did a dose response giving one, two, and three Ariva at a time, found that dose was dose proportional and that as you pushed the number of tablets upwards, you got significantly more nausea. Their conclusion was that the product did reduce craving, but had significant nauseating effects,

which made us feel very good as that was part of the plan.

Mendoza-Baumgart did a study of Exalt and Ariva in smokers, crossing smokers over in a two-way crossover, looking at whether their cotinine went down -- it did -- whether their carbon monoxide went down -- it did -- and whether their urinary mitogens, the NNAL levels went down. They did.

Gray did a multiple session human study in which they first -- people first underwent a laboratory session in which they had four-hour test sessions with actives or placebo, and then a series of four or five-day test sessions using their own brand of smokeless, Stonewall, General Snus, or no smokeless tobacco at all, placebo condition. Outcome measures were plasma nicotine, craving, urinary cotinine, and NNAL.

Own brand and General delivered much more nicotine than Stonewall, 25 nanograms per mil versus 5, and there was a trend toward less craving with the higher nicotine products. Results for the

five-day session showed that all the SLT products reduced craving and anxiety relative to no tobacco, with cotinine and NNAL levels significantly lower for Stonewall than for the full strength moist snuff products.

Carpenter and Gray conducted a naturalistic study trying to mimic what would happen if someone went into the store and bought one of the products. Instructions -- and I would have loved to have written this protocol -- were very simple. "Read the label and you should use it at least every two hours." I've never seen a study where those kinds of instructions were given.

Both groups' outcomes were cigarette use, carbon monoxide, product use and readiness to quit, as well as a self-efficacy measure. Both groups continued to use tobacco, with the PREP group using significantly fewer cigarettes per day, about a 40 percent reduction. The PREP group reported greater self-efficacy and readiness to make a quit attempt in the next six months.

Tom Eissenberg's group did a study in

smokers, consisted of four five-day periods, presented in random order, in which subjects used their own cigarette, Camel Snus, Ariva, or no tobacco. Outcome measures were CO, cotinine, NNAL, nicotine levels, subjective ratings of nicotine effect, and craving. CO fell to baseline for all SLT conditions and no tobacco. Cotinine fell on the rank order, no tobacco, least. Ariva, the rate is declined. Ariva next, Camel next, and Own brand least.

NNAL was unchanged for Own brand, and Camel fell for no-T in Ariva. Craving, no tobacco-most craving, Own brand-least craving. Pleasure rank order, own brand-most craving and liking, Camel-least. Overall, these investigators were not impressed with the degree to which either PREP substituted for own brand cigarettes.

O'Connor conducted a study of cigarette smokers not interested in quitting who participated in the trial of Camel Snus, Marlboro Snus, and Stonewall, and Commit. Subjects tried each product for a week and then used their preferred product

for an additional week.

Outcomes were product preference, cigarette smoke, cotinine, and carbon monoxide. Commit was most liked, Stonewall was least liked. In terms of choice, Commit was most often chosen, Stonewall was least often chosen.

DR. SAMET: Excuse me. Just in the interest of time, we've actually been provided with --

DR. WRIGHT: Copies of those?

DR. SAMET: -- all of these studies.

DR. WRIGHT: Okay.

DR. SAMET: And probably many of us have read them already. So I would like to --

DR. WRIGHT: Then I will move right along.

DR. SAMET: -- move along, yes.

DR. WRIGHT: Okay. Hatsukami study, you've seen that. If you have read that, you've got those results. We've already talked about Parascandola.

The conclusions from human studies are that the dissolvable tobacco products deliver like NRT. The products are of moderate interest smokers and of greatest interest to smokers with health

concerns.

Most smokers did not like Ariva and Stonewall as much as cigarettes, but found them less aversive. Ariva and Stonewall are less liked, less chosen, and pose less abuse risk in human testing than OTC NRT products.

Moving on to health effects. The risks of smokeless tobacco have been exhaustively examined. All SLT is addictive, all SLT has cardiovascular risks, all SLT has metabolic risks, especially in patients with hypertension and diabetes. Peripheral vascular disease is particularly bad if you're using any form of tobacco product.

Aerodigestive cancer, there is still controversy in the literature as to whether there is a risk for low nitrosamine tobacco products. But the most common non-behavioral adverse event for these products are tooth loss and periodontal disease for chewing tobacco products with high sugar content and smokeless leukoplakia for high nicotine, high pH snuffs.

I don't think we need to go over chewing

tobacco. It will do serious damage to someone's oral health.

Excuse me. Have they received the dissolvable tobacco comments? Okay. Because we cover this very extensively in the dissolvable tobacco comments that we made. There's about eight pages on leukoplakia and its causes and cures.

Leukoplakia is a reversible lesion and it's related to how long you keep a product with how much nicotine at what pH next to your mucosa. Third world products are extremely bad. NRT products have not shown any significant leukoplakia. And controlling the nicotine dose and pH of the product have been shown to prevent or markedly reduce the risk of leukoplakia and/or reverse the lesion.

There has been -- and this was asked earlier. There has been a pre-clinical study in a model in an attempt to look at oral health for products in this class. This was a rat lip canal model, where the rat has had a tube formed in their lip. And what they found was what we expected, and

that is that the higher the nicotine content and the higher the TSNA content, the more likely dysplasia was to occur at the site of chronic application. But these are really secondary points and well known.

The major risk with respect to these products is concern about pediatric safety. Despite the efforts that we made, we needed to assure ourselves that our products were not posing a pediatric risk.

This is the average per year for 2002 to 2008 for the Poison Control Center's annual reports. And what you'll see is that there are about 5,000 pediatric cigarette toxin exposures a year, and that's lower for chewing tobacco, a little lower for snuff, lower for butts, cigars occur, and NRT products actually are responsible for some significant number of exposures.

So how much does the product look like candy? We solved that by sending a group of trained candy buyers into the local stores and collected as much candy as we could find. Our

concerns were that benign attractive packaging which may be confused with candy containers might reduce necessary caution, increase misjudgment, or mask the risk of accidental use.

We think that the possibility of product ingestion by children requires attention to the package design and product appearance. The major distinction between the packaging and labeling for NRT and smokeless tobacco products are the container shape and product warnings.

Can anyone here identify the NRT product in the photo? I can't, and I made the photo.

How about this one? Which one is the NRT 4-milligram product? Please identify the dissolvable tobacco product and the NRT product in this collection of jelly beans.

We think this risk is real and it must be managed. As has already been said, we think child-resistant packaging is a must for this class of products. The reason that we know our products are resistant enough is that we get multiple complaints from adults that they have trouble getting into the

package.

We have received no comments with respect to pediatric safety in 10 years of marketing, but we also know that Bob Temple said that the absence of evidence is not evidence of absence. So we went to the American Association of Poison Control Centers through the Rocky Mountain Poison Control Center, and they had begun coding dissolvable tobacco products in 2009 and 2010.

So we submitted -- we asked them what did they find, and we have submitted that to this committee and to the FDA. For the period of use, in which 12 million units of Ariva and Stonewall were sold, there were three dissolvable tobacco cases. They were minor cases, which there was no toxicity and they resolved with home care. In that same period, there were 6,000 cigarette exposures and 1300 NRT toxicity cases. If there is a poison candy problem, it is not with Star's products.

Lessons learned. Child-resistant packaging is appropriate and needed. Nothing will make dissolvable tobacco taste attractive if it has

adequate nicotine loading. The products need to deliver at least 1 and a half to 2 and a half milligrams per dose unit for smokers. The TSNA and pH levels can be made very low, and they pose no risk to youth that we have been able to detect in a decade of sales. But the risk-benefit of these products is dependent on how they're made, promoted, marketed, and managed.

I'd like to talk for two seconds about the World Health Organization standards. The WHO tobacco group has recommended that the total NNN and NNK for a product of this class be two parts per million, that's 2,000 parts per billion, or five parts per billion for benzo(a)pyrene.

We've given you the results of the testing that we did on the dissolvable tobacco products that we could buy, and you will note that all of them are well below these limits. Thus, we make a recommendation to the committee that dissolvable tobacco products have no more than one part per million NNN/NNK per dry weight and no more than two parts per billion BaP.

We also think you need to express the toxin levels per milligram of nicotine. What you see in the top graph is the toxin levels, BaP, NNK and NNN, per cigarette for very low tar, low tar, moderate tar, high tar, and very high tar cigarettes. And if you have the left-hand graph only, you would come to the conclusion that the low tar products were safer, unless you were using them to get nicotine and you smoked more of them harder until you got adequate nicotine, a phenomenon called compensation.

If you look at the toxins per milligram nicotine, what you find is that the low tar products actually deliver more toxin to the user for the same amount of nicotine obtained. We think that expressing toxin levels per milligram nicotine for smokeless tobacco products is a very good idea.

We think pH and nicotine content are important. We think that there needs to be at least 1 milligram per unit, and probably no more than 5 milligrams per unit. We think the pH should not be less than 6.5, as such products deliver no

nicotine, but no more than 8, because those products were associated with leukoplakia in snus studies.

For part 2, our conclusion is that tobacco is toxic and never can be made safe. The comparator is continuing to smoke. Tobacco is addicting and will always be so, and there is no safe tobacco product. But we do think that some products are more toxic than others.

Dissolvable tobacco products appeal to middle-aged smokers seeking a less toxic alternative to continuing smoking. They have a low abuse liability in the studies reviewed and pose little risk of widespread use based on sales to date. There is always a risk of pediatric toxicity, but this risk is less than current OTC NRT products and can be safely managed with appropriate packaging, labeling, and marketing.

DR. SAMET: Thank you.

Just a quick question on the pediatric data and the poison control data. The missing piece there of information, of course, is the

denominator, and, of course, we would expect far more exposures to cigarettes, for example, or perhaps NRT.

What we're really interested in is the rate of accidental exposure or ingestion. And with such small penetration right now of your products or dissolvables, in general, it would be very difficult to estimate that.

I think what is really of interest is whether -- if there were wider-spread usage of this, what might be the extent of the problem. So I think we're still back at the absence of evidence probably, given the relatively small denominator of exposures for children.

So I think we have to be careful in interpreting the data available in that light. It's what we have, of course, but it's very small and, let's say, limited in what it might -- how informative it might be.

DR. WRIGHT: Well, we don't have the data because we don't have access to the data, but I believe the FDA can give you the amount of NRT that

is used, that is made and used, and you probably will be able to do some of that calculation.

But I will also say that there is a dichotomy, from a scientific perspective, what the relative rate for the two products would be is useful and helpful, and it's what a toxicologist needs to know.

In terms of the population at large, the question is what is the actual rate of the events for the populations at risk. Frankly, I'm going to tell you, from my perspective, you are not going to see, with any amount of marketing, an explosion of use of this class of products. I think the data is relatively compelling, that compared to a cigarette, these don't do it. They are useful, they are helpful, people can switch to them, but they don't have the same traction.

DR. SAMET: And, again, my comment was far more limited and simply speaking to interpretation of the pediatric data.

Neal?

DR. BENOWITZ: A couple questions. One is

how much nicotine is absorbed buccally versus swallowed and absorbed orally?

DR. WRIGHT: Don't know.

DR. BENOWITZ: It would be a very simple study to do.

DR. WRIGHT: Yes. And if we made more profit, we would probably do it.

[Laughter.]

DR. BENOWITZ: My guess is, on the PK and from knowledge about nicotine PK in general, that most of it is probably swallowed and absorbed orally.

The reason why that's a concern is that normally the systemic dose, when you swallow orally, is limited by high first pass, which is pretty effective for most people. But we also know that there's a subset of people who are cytochrome P450 2A6 poor metabolizers who don't metabolize very well and would have high bioavailability.

So there could, in fact, be a subset of people who would be quite susceptible to -- the kid, say, who swallowed it who might be susceptible

to poison. I'm not saying that you have any data, but I'm saying this is something that I think is a real issue.

The second question to bring up has to do with the titration concept and normalizing per milligram of nicotine. This makes sense for cigarettes because people can titrate how they smoke a cigarette and for a single cigarette, they can get any amount of nicotine according to how they smoke it. It's not true for these products. You take a product and you get the amount of nicotine.

So for this kind of product, where you're not self-titrating the dose, it seems to me that the amount per dose is actually more important than the amount per milligram nicotine.

DR. WRIGHT: I agree completely. The reason that we want the amount per milligram nicotine is to prevent cheating. If I was trying to market a dissolvable that I wanted to look really good, I'd give it a great flavor, and I'd put about a tenth of a milligram of nicotine in it. That's the only

reason.

DR. SAMET: Dan?

DR. HECK: Just a piece of information more than a question, if you will. The American Association for Poison Control Centers, I guess their most recent report is 2009 data available, and data 2010 I guess is on the website. And I might mention, too, that that organization is beginning to record in the tobacco products category in terms of incidents.

The present listings include snuff, cigarette butts, cigars, other products, and unknown types. I think going forward, maybe beginning this year, the category of dissolvables is a separate listing, so we'll begin to collect more definitive data. Just as an aside, other categories, including e-cigarette cartridges and e-cigarette filler fluid are also being recorded now as independent data tracks.

I'll mention, also, briefly, that there is a paper being presented at the clinical tox meeting in September -- I have the abstract

here -- reporting pediatric ingestions of dissolvable tobacco products in one state poison control center over a period of years. Again, the identity of these as true dissolvables is a little uncertain due to the manner of recording. Fourteen incidents were recorded, none of which had a serious outcome, and the authors concluded that a real serious complication seemed unlikely with this category of product.

I'll be glad to provide that abstract. We should have the poster presentation in the next few months.

DR. SAMET: Okay. Thank you.

Yes, Fred?

DR. PAMPEL: It looks like, according to one of these studies, that respondents preferred Commit over Stonewall. Yet, one of the responses to the Federal Register in the docket said that he was able to quit with -- I think it was Stonewall, but not with NRT, and suggested that there are some aspects of the tobacco component of Stonewall that were more beneficial, that he liked more, more

suitable for people who used to smoke.

So I'm trying to get the sense of what the non-nicotine products in Ariva or Stonewall bring to users.

Does that make it more attractive to them or what?

DR. WRIGHT: I can't answer that. We have done -- and I'll show you in the next presentation -- a head-to-head comparison between Commit and Stonewall, and we couldn't see any difference.

Now, what was very clear, and I'll show that data to you in a little bit from Dorothy Hatsukami's study and from one of the studies that I showed you, people develop strong preferences for one of these over the other. And I cannot explain that scientifically, but it's really true. And I have no idea why that might be true or why people like Coke versus Pepsi.

DR. SAMET: Robert?

DR. BALSTER: I've understood I'm getting your perspective on the relevance of these human

laboratory type studies that you reviewed for our assessment of the abuse liability of the dissolvable products. In those studies, one type of them, they take regular smokers who are abstained for overnight and then they give them one opportunity to use, say, a smokeless product, and the products don't do very much at all in terms of suppressing tobacco withdrawal in those studies, for example, from Eissenberg's lab.

In actual fact, the nicotinized cigarettes do a little better job, and that group has interpreted those sort of results as saying, well, sure, you have a smoker that has all of the queues associated with smoke. They come in and they take a pill, and it just doesn't have a very good effect in suppressing nicotine withdrawal.

So they've taken these studies now to typically five days, where this would give an person an opportunity over five days, presumably, to learn maybe that using the product for five days, they might be able to get some withdrawal relief. And even in those studies, by and large,

they are not that great. I think you just said that. They are not that great in essentially replacing Own brand cigarettes in terms of withdrawal suppression.

Does Star have any data or any even ideas about really how long of a use period it takes for people to sort of reach some sort of asymptotic understanding of how those products interact with their tobacco dependence and that?

I mean, how long does it take people to learn to use them in a way that reaches their pinnacle of satisfaction?

DR. WRIGHT: That would be truly subjective comments that have been called in to our line, and that's a couple of weeks to learn how to use these products, learn how to use them so you don't get the nausea, learn how to use them so that you don't take too much and get the hiccups; a couple weeks.

DR. BALSTER: The corollary to that would be then really -- in effect, to have a study design that would give you a full picture of what the, let's just say, replacement value is of these

products in a heavy smoker, you would recommend that there be at least a two to three-week trial period of time in which to see what the results would really be.

DR. WRIGHT: Well, there are two questions. One is are you interested in what their value as a replacement product for a smoker is, that's a valid scientific question. But there's the other issue of how much impact do they have and how likely are they to be abused. And, traditionally, single-dose studies have been the studies that we've done for impact kind of studies. And all I was referring to when I talked about abuse liability was these certainly did not seem to be any worse, and, in most of the studies, seemed to have less impact than many of the other forms of tobacco.

DR. BALSTER: I agree with you, that, traditionally, single-dose studies have done a good job. And I'm just questioning whether, in this particular product category, that is the right way to think about it. I think there could be, after we thought about it, in terms of a little bit

longer period of experimentation or use to achieve some kind of asymptotic level of what people's --

DR. WRIGHT: I smell a grant.

[Laughter.]

DR. SAMET: Patricia, did you have a question?

DR. NEZ HENDERSON: I just had a question about the health effects. Did you find any differences for impotence?

DR. WRIGHT: I would have to ask that question.

Have we had a single call about male sexual dysfunction?

FEMALE VOICE: No.

DR. WRIGHT: No.

DR. SAMET: Mark, any questions?

DR. CLANTON: Yes. I do have a question. It's back to the list of criteria for potential poisonings, with that childproof package or child-resistant package being number one. I think number two had to do with the taste of the product, and I think the speaker, and maybe other speakers, talked

about how maybe unpalatable these products are or might be engineered so that they won't appeal to kids.

I just wanted to offer up, as a pediatrician who has treated poison, as well as other pediatricians' experience, that kids tend to ingest things based on color as opposed to taste. Kids have ingested caustic substances that cause esophageal burns, and, in fact, the number one cause of these sorts of poisonings are actually household cleaning products, which are incredibly nasty.

So I would offer up that you might want to be very careful about talking about unpalatable taste as a reason why kids would not ingest these substances, when, in fact, they ingest them all the time.

DR. WRIGHT: My response to that is that the unpalatable taste has to do with initiation of use in older adolescents. I agree with you. Pediatric poison occurs with the most ghastly-tasting things imaginable.

DR. CLANTON: Absolutely. And one last point. I can't remember who asked the question about if the container, which is child-resistant, is sort of opened and left open -- which, by the way, is yet another source of pediatric poisoning. It's actually grandparents who may be supervising kids, and once they get that darn resistant package open, it's often left open and kids can get into that.

But the issue has to do with dose and minimal lethal dose of nicotine for kids, and the minimal lethal dose is about 1 milligram per kilogram of body weight.

So I just want to make the point that we may end up seeing some deaths, although we may not see very many poisonings at a minimal level, but could see deaths if kids simply down a bottle, given that most of those poisonings occur between 6 months and 24 months of age. It's fairly easy to achieve that 1 milligram per kilogram minimal lethal dose. So it's just something else to consider as you look at the safety profile for pediatrics of these

products.

DR. WRIGHT: I certainly will, but that involves somebody else's product, so I don't think I'll answer for them.

DR. SAMET: Okay. I think what we should probably do -- we're not going to have a break, in the interest of time. So let me ask. Are you prepared -- the next presentation would be of value. Do you want to --

DR. WRIGHT: Rock and roll.

DR. SAMET: You're ready to go.

[Laughter.]

DR. SAMET: Okay. Go for it.

Industry Presentation - Curtis Wright

DR. WRIGHT: Since you have advised me that you have the papers, I am only going to briefly touch on them, because I am assuming that you will review them at your leisure.

We described the products, we described the data showing what's in it. We did a couple of studies. As I said, we are not a financial giant.

Our study of Stonewall we did head-to-head

with Commit specifically to address the question that was asked, is there something special and different about these, because we had hoped that Stonewall would have a better subjective effect than Commit. So we rounded up the usual suspects, men and women in their 40s and 50s who had been smoking for 30 years, who weren't terribly interested in quitting, and we gave them Commit or a Commit placebo, or we gave them Stonewall or a Stonewall placebo. And what we found was that both worked in terms of reducing nicotine craving, as measured by the QSU and MBRS, and we couldn't see any difference between the two. If anything, Commit maybe had a little bit better pharmacokinetics and worked a little bit better.

However, we did reaffirm what we thought about the toxicity, because these were cigarette -- and this was the other question that was asked, initiation of use and getting used to the product. These were pretty heavy cigarette smokers, and yet they still had significant nausea, dyspepsia, mouth burning, and hiccups as a result

of using the product.

We already talked about why people try Ariva and Stonewall. We talked about Caraballo. We talked about O'Hegarty. Initiation is by smokers and SLT users in the 30 to 50-year-old age group who are attracted by curiosity. These have not proved to be significantly more attractive than cigarettes.

In terms of migration, we find that most of the women and the light smokers among the men prefer Ariva. Heavy smokers and smokeless tobacco users use Stonewall. Usage is about four to six lozenges a day. We do not know how much dual use there is, although we have a little bit of information on that. But most dual use is people who are in environments where they can't smoke, or don't want to smoke, or they don't want to expose their children to smoke, like in a car, and they use the product.

There has been one cessation study that we could find using our product, and that was done by Dorothy Hatsukami's group, and she took smokers who

were motivated to quit -- I don't know what she does in Minnesota, but she does something to them -- allow them to test the four PREPs, and then had them attempt cessation using the PREP of their choice. She offered them four, and General Snus was not accepted by anybody.

What you see is a curve that's actually very similar for all of these products to NRT. There's a rapid initial relapse. Camel Snus performed the best. Stonewall and Marlboro Snus were about the same, and Ariva was definitely statistically inferior. And the rank ordering is the rank ordering of their nicotine content.

For products of this class that have a long mouth residence time and don't have a high buffer capacity, it's not as much the free nicotine as the total nicotine content if the mouth's buffer capacity has a chance to work on the product.

We've talked about Carpenter and Gray. We've talked about O'Connor and self-efficacy.

I want to talk a little bit about dual use. Most of the dual use concern has to do with studies

that were done with conventional smokeless tobacco products. There is relatively little data on low nitrosamine products, and there is even some problem with the Swedish data on snus, because low nitrosamine products are a phenomenon of 1995 to 2000 and beyond. So there is not 20, 30, 40 years' worth of epidemiologic experience. Studies of dual use in Sweden do not show as much of a dual use increased harm effect as in the United States.

I will remind you of the Levy meta-analysis and the Royal College of Physicians, who reached the conclusion that low nitrosamine smokeless tobacco products, of which dissolvable tobacco products are a subset, marketed under regulations, but with relevant health claims, would not impede the decline in overall smoking prevalence and that the introduction of a well regulated product is expected to reduced smoking and only modestly increase SLT use. Now, you can read Levy for yourself and decide on the worthiness of the authors.

There have been multiple peer-reviewed

publications on snus and SLT, but I believe that will be covered by compatriot at the other company, so I'm not going to talk you through these.

The real issue is that 40 years ago, we made a mistake. Based on the science that my high school teacher showed me, where he smoked a cigarette and blew it through a handkerchief and said see the yellow stain, we launched in this country marketing campaigns for cigarettes based on filters being better, and the less tar and nicotine, the safer the cigarette. And that took us down a road that led nowhere.

We have been working -- and when I say "we," the tobacco industry and the scientific community have been working on -- both have been working on the concept of a potentially reduced exposure product for 20 years. Effects have been minimal to date, and the reason is that what is said about these products and how it is said to whom matters.

We think this is a safe place for you to engage in some labeling exercises. We think it's way past time to put the toxin contents on the

label. Because the U.S. Surgeon General, in 2000, said, and we can't agree more, "As with all other consumer products, adult users of tobacco should be fully informed of the product's ingredients and additives. And of any known toxicity, when used as intended, additionally, as with other consumer products, the manufactured tobacco products should be no more harmful than necessary given available technology."

DR. SAMET: Okay. Thank you.

Questions? Neal?

DR. BENOWITZ: To address your dual use and the panel of experts, I was wondering if you've read the paper written by Pam Ling and Stanton Glantz -- I forgot who the first author was -- from UCSF looking at smokeless tobacco and its impact. And they modeled the impact based on its intrinsic risk versus its potential role in maintaining cigarette smoking in people who would otherwise quit. And they concluded that the biggest harm for smokeless tobacco was sustaining tobacco use in people who might otherwise quit.

Have you read that, and how does that synch with this panel of expert analysis?

DR. WRIGHT: I'm afraid that Levy is going to have to stand on his own. I wouldn't speak for someone else's meta-analysis.

Have I read that paper? Yes, I did. I think you're more familiar with it than I am given it's regionality.

There is a dilemma that I don't know how to solve, and I am going to be very honest about it. There is the big social concern, population as a whole risk, and there is the problem of the individual. And they are hard to balance because for the individual, the consequences are severe. For the population, the consequences are diluted across the population of use.

The people who I think benefit from dissolvable tobacco products are individuals -- and I know them and you know them, too, because some of them are our colleagues -- who have tried everything up to and including being locked up in a rehab to quit smoking and have failed. And they

exist.

The other population that I'm deeply concerned about are the populations that don't have access. They just don't have access, or they don't believe us when we talk about health effects, or they're not motivated at all by health concerns. I think there's going to have to be multiple pathways out. I think there's going to have to be multiple ways for people to get out -- for this society to get out of this fix it's gotten itself into with tobacco.

I am not enamored of conventional moist snuff. I think it's got poor dose control. I think it's more toxic than it needs to be, and I think it provides way too much psychoactive kick. And so I don't know how to model the effect of dissolvable tobaccos because I don't know what their penetration is going to be. So far, it's not been very impressive.

DR. SAMET: Okay. Other questions? Yes, Patricia?

DR. NEZ HENDERSON: You mentioned three

times in your presentations that your company is not doing well financially. Why is it still in the business? You must be doing well.

DR. WRIGHT: Okay. Well, first of all, Star Scientific is not only involved in dissolvable tobacco products. The dissolvable tobacco products are the products of Star Tobacco, a subsidiary of Star Scientific. Star Scientific has some other products that are doing rather nicely.

Why do we keep Star Tobacco open would have to be addressed to the board of directors and to the president. But I do know that I have sat with them and I have talked with them. And there is a real concern for trying to make and maintain access to what the company and its scientists honestly believe is a less toxic product for the people who are very loyal users and who say "I don't have to smoke anymore."

Are they still facing tobacco risks? Sure. Would it be better for them to quit? Absolutely. But I think there's a population you are not going to get off nicotine in this life.

DR. SAMET: Sort of along the same line, I think we saw some figures, I think they were yours, about tons of product. And do you have any estimate of the number of people who might have actually used your products, numbers as opposed to amount of product produced?

DR. WRIGHT: You are going to have to ask that of the marketing department.

FEMALE VOICE: Roughly three to four million.

DR. SAMET: Have tried perhaps.

FEMALE VOICE: Since 2001.

DR. SAMET: Since 2001. Okay. That's helpful.

Let's see. Other questions?

Mark?

DR. CLANTON: No, no additional questions.

DR. SAMET: Okay. And anyone else?

[No response.]

DR. SAMET: Okay. Thank you, Dr. Wright.

Okay. Then we'll move on to the presentation by Dr. Geoffrey Curtin from R.J.

Reynolds Tobacco Company.

Industry Presentation - Geoffrey Curtin

DR. CURTIN: Good afternoon. My name is Geoff Curtin. I'm a principal scientist with the regulatory oversight group of R.J. Reynolds Tobacco Company. And I appreciate the opportunity to speak with you this afternoon about the population level effects associated with smokeless tobacco and, where available, dissolvable tobacco products.

So I'm going to break this talk down into three parts. The first part I'll spend kind of outlining what our perception is on the appropriate context for examining the nature and impact of dissolvable tobacco products on public health, and then kind of summarize the available science regarding population level effects associated with increased use of smokeless tobacco products, including dissolvable products, and then some information on modeling for estimating the population level benefits and deficits with increased smokeless tobacco use, which may address some questions by Dr. Benowitz.

First and foremost, what we've heard today is dissolvable tobacco products are best characterized as low nitrosamine smokeless tobacco products. The population level effects or unintended consequences as they appear in the literature are that products such as dissolvable tobacco will be a starter product and have a gateway effect; that dual use will occur versus complete product switching; and, that dissolvable tobacco will facilitate continued smoking or continued tobacco use.

We believe that any examination of the population level effects associated with smokeless tobacco products or dissolvable tobacco products must consider the associated risk profiles. Disease risk is significantly influenced by product type, as well as the frequency, duration, and manner of use. And while no tobacco product has been shown to be safe, the risks associated with smokeless tobacco and/or nicotine products are significantly less than cigarettes.

So this is relative risk data from the

Cancer Prevention II study. The red bars represent relative risk for smokers compared to never tobacco users from the Surgeon General 1989 report. The green represents the oral or smokeless tobacco users from the Henley, et al, 2005 report.

As you can see, for lung cancer, respiratory disease, heart disease, or pharyngeal cancer, significant increases for smokers compared to never users. For smokeless tobacco, the increases are limited to lung cancer and heart disease. The lung cancer in almost any other study hasn't been replicated, and because CPS-II is the largest survey of its kind, it overwhelms meta-analyses and other things.

We didn't put pancreatic cancer on this list. I know it is a concern among public health. There are a couple studies that would suggest an increased relative risk for pancreatic cancer among smokeless tobacco users.

First of all, the risk for smokers is about two. A couple studies in Sweden suggest that maybe one, one and a half for smokeless tobacco users.

But the studies in the U.S. suggest no increased risk and meta-analyses that include all these studies suggest no increased risk to never tobacco users. So that's why it's not on this chart.

The important thing here is the substantial reductions in mortality risk for smokeless tobacco use are supported by the same data that are used to establish disease risk for smoking.

So big difference in risk. This has been called the risk continuum or continuum of risk, where you'd have cigarettes on one end presenting the most risk to tobacco users, and smokeless tobacco and nicotine products on the lower end. The low nitrosamine smokeless tobacco products would be at the low end of smokeless, towards the nicotine products. But we've had a number of public health organizations that have recognized this pronounced continuum of risk, as well as the potential for harm reduction with complete product switching. And most of these organizations have looked at the low nitrosamine products versus all smokeless products, and those would include the

Royal College of Physicians, World Health Organization, the Strategic Dialogue on Tobacco Harm Reduction Group.

So leading with the strategic group, in 2009, they published a paper indicating that smoking is undoubtedly more hazardous than various forms of smokeless tobacco. In fact, smokeless tobacco is not associated with many of the smoking-related cancers or pulmonary disease. No smoke exposure, no lung disease.

A nine-member panel of experts, tobacco epidemiologists, got together in 2004, or convened in 2004, and looked at the relative risks of cigarettes and low nitrosamine smokeless tobacco, and suggested that the median total mortality relative risk was about 5 or 10 percent of that for low nitrosamine smokeless tobacco compared to smoking.

There were significant reductions in lung cancer, greater than 96 percent. You would assume that number would be the same for respiratory disease, and a 90 percent reduction in heart

disease.

Now, importantly, the panel assumed that smokeless tobacco use was limited to the low nitrosamine smokeless tobacco and, notably, pointed out dissolvables and snus. And the estimates were based, in part, on epidemiological studies from Sweden.

So as I said before, the significantly lower risk associated with smokeless tobacco use compared to smoking must be considered when examining population level effects. After all, 80 to 90 percent of tobacco users in the U.S. are cigarette smokers.

When I mentioned that the available studies from Sweden were considered in these type analyses, for those that are not aware of it, studies in Sweden demonstrate the potential to reduce smoking-attributable disease with smokeless tobacco use. So Sweden is the only country, the only developed nation, to achieve the WHO target of reducing smoking prevalence to less than 20 percent.

During this same period, Swedish men -- and

this is a male-only phenomena in Sweden up until about early or mid 2000s -- exhibited substantial decreases in smoking-attributable disease, and, that is, the lowest incidence of lung cancer among any of the developed nations, a continued low incidence of oral cancer by international standards, and significant improvements in cardiovascular health.

So what we have on this graph is the green line represents the daily snus consumption among Swedish males from 1976 to 2000, the red line is the daily smoking, and the blue line is the combined daily smokeless and smoking.

What you see is from the period of 1976 to 2002, snus use increased from about 10 percent to about 23 percent, smoking declined from 40 percent to about 25 percent, and you had a reduction in total tobacco use.

One of the reasons I showed this, because many people may be aware of these trends, but there's been a lot of discussion about this data. This data is from Foulds, et al, 2003, but it

matches very well with the Swedish statistics data. Yet, I continue to see at some meetings where people are suggesting that smoking hasn't changed for males in Sweden in the last 20 years and that the smoking prevalence is up around 25 or 30 percent, and that's just a mischaracterization of the data.

So what could that result in? And one of the studies that was done, again, by Foulds, looked at what the lung cancer rates were for Swedish females and males, as well as Norwegian males. So what you have is this decrease in male smoking starting about 1976 and going down through 2002, and it goes from about 40 percent to 15 percent. And with some lag, you see a leveling and then eventual decrease in male lung cancer rates.

As I mentioned before, this is primarily a male phenomenon and you haven't seen that kind of reduction in smoking in females. Hence, you've seen the continued rise of female lung cancer rates. For comparison, next door in Norway, you haven't seen this kind of switching or reduction in

smoking either. Those trends were about the same through '76-'80 and they continued to go up.

So moving to the second part of the talk, many opponents of advocating product switching to reduce smoking-attributable risk often cite concerns regarding dual use and gateway effect. This is what I was talking about before about unintended consequences. And these debates have been around in the literature for possibly 10 years and they are being now applied to dissolvable tobacco products, given that they are a low nitrosamine product.

That is, specifically, that dual use will not be associated with reduced smoking frequency, but will instead increase toxicant exposure and, therefore, risk for disease; that dual use may facilitate continued smoking; and, that smokeless tobacco use increases smoking initiation. However, and there is a lot of data on this, the available data do not support these hypotheses regarding these unintended consequences, and that's what I'll spend a couple of minutes talking about.

So, first of all, there is a lot of epidemiology on smoking and smokeless tobacco use and comparison of the two in the same studies. There are very few studies where you can actually look at dual use among a population. These are summarized here. At the end of the day, you basically have no increase for all cancers, oral cancer, heart disease, all cardiovascular disease when you compare dual users to exclusive smokers.

The same can be true for clinical events, such as stroke and myocardial infarction. And what I should have pointed out before is really the risk, as was pointed out by the American Heart Association policy statement -- was the real risk for smokeless tobacco products is not incidence of cardiovascular disease, but acute events, acute MI, acute stroke. That's where the real potential increase is. Again, these would be much less than smoking, but that's where they differ from never users.

So the data from Sweden -- and I've broken it down into data from Sweden and data from the

U.S. But for Sweden, dual users are clearly more likely to reduce smoking frequency, and, that is, smoke fewer cigarettes per day, compared to exclusive smokers. So some work that was done by Lund out of Norway suggested that dual use was a positive predictor, with an odds ratio of 3.1 -- and I will only have odds ratios in this talk if they were statistically significant -- in regression analyses of greatly reduced cigarette consumption.

Caldwell, et al, suggested that smokeless tobacco provides a sufficient substitute for nicotine to significantly reduce craving and allow smoking reduction of approximately 40 percent. And then there was an inverse relationship between dual use, that is, weekly smokeless tobacco consumption, and cigarettes per day for those people that smoke 20 or fewer -- I think just fewer than 20 cigarettes per day. This is all we could find from Sweden, but it's incredibly consistent.

In the U.S., the data is lagging some behind compared to Sweden given the prevalence of use of

smokeless tobacco in Sweden for many decades. There are three pilot studies that were talked about earlier that have been recently published.

Just to summarize those, because these all touch on dissolvables, smokers interested in quitting, reduces their smoking frequency approximately 40 percent; that is, they smoke 40 percent fewer cigarettes per day. During the dissolvable tobacco sampling period, it did allow ad libitum smoking. That's Hatsukami 2011.

Shortly before that, smokers not interested in quitting reduced cigarette consumption about 25 percent during a trial of smokeless and nicotine products. That trial did include dissolvable tobacco products and ad libitum smoking was allowed.

Based on the daily consumption patterns, they suggested that the stable level of substitution was consistent with smokers preferring a gradual shift versus an immediate changeover to quitting, and that would be similar to NRTs.

Then in 2010, and I think this study has

been talked about, as well, Carpenter and Gray reported that smokers not interested in quitting partially substitute the dissolvable tobacco for regular smoking. Again, there was no requirement to abstain from smoking. Yet, the smoking frequency was reduced 40 percent.

So, again, these are all small pilot studies, short in duration, small number of people, but very encouraging. My understanding is that with this publication and with this data, Carpenter and Gray used this data to get funding for a very large one-year study that will have over a thousand participants.

So what would be the effect of reduced smoking frequency? Reduced smoking frequency among dual users likely results in reduced toxicant exposure. I think some data from CDC was pointed to in one of the earlier presentations. But it has been shown from a compilation of a number of studies that product-specific concentrations of NNK, which is a TNSA carcinogen, closely parallel urine concentrations of that of NNAL, which is the

NNK metabolites in tobacco users. It was concluded from that paper that there was a strong potential for smokers to dramatically reduce toxicant exposure by switching to these low nitrosamine smokeless tobacco products.

From the same lab, around the same time, they reported significant reductions in carbon monoxide, total cotinine, which is a nicotine metabolite, and total NNAL levels during dissolvable tobacco substitution for regular smoking, and they concluded that the low nitrosamine smokeless tobacco products had the potential to reduce toxicant exposure but also may show promise for reducing individual risk.

So dual users, whether they're more likely to quit or not, the data from Sweden are quite compelling. Dual users are more likely to quit smoking compared to exclusive smokers. So as you look across these studies, some of them from Norway, some of them from Sweden, you see that there's a number of studies that report increased odds of being a former smoker or quitting compared

to exclusive smokers, and then some analysis done by Furberg 2008 looking at main effects, showing that dual use was the strongest independent correlate of smoking cessation. All these studies were fairly large studies, either national survey data or national representative populations.

I'm sorry, I forgot to mention it before. The studies I put at the bottom in brackets are studies that probably should be considered as you go through and do this analysis. These studies actually rise to the top. There were some deficiencies with those. But just to be complete, we wanted to point those out.

So for this, all these studies pretty much agree with this finding.

In the U.S., again, you don't have a lot of dual users. So this data is just starting to develop, but the trends are very similar in the U.S. to what we see in Sweden. So, for example, the Carpenter and Gray small pilot study I talked about a moment ago, dual use including dissolvable tobacco significantly increased the measures of

readiness to quit and self-efficacy to quit in a pilot study; again, small study, short duration, but a positive finding.

Tomar, et al, 2010 reported that dual use significantly increased past year quit attempts, and, also, those seriously considering quitting or even all levels of interest in quitting, and that daily dual users were more likely to be former smokers in the national surveys they looked at. They looked at four national surveys. I believe these findings were from the 2006-2007 II-SCPS.

Also, Kozlowski 2003, those people that were cigarette initiators and then moved to smokeless tobacco -- so they're dual users, they started with cigarettes, so you would infer -- the reason this was looked at is they may be using smokeless tobacco to quit -- were twofold more likely to have quit smoking in a national survey compared to exclusive smokers.

So for Sweden, the evidence of a gateway effect, and, that is, does smokeless tobacco use drive increased smoking initiation. Again, the

evidence is overwhelming. In fact, people have looked at this data and said that in Sweden, at least, smokeless tobacco is a gateway away from smoking and not toward smoking. So you've got a number of studies that have shown decreased odds for initiating daily smoking compared to -- for smokeless tobacco users compared to non-tobacco users.

The study that's actually in italics, the reason it was highlighted is I wanted to point out a trend that you see in Sweden that you might be starting to see in the U.S., and that is that younger male tobacco users, or those that may be prone to tobacco use based on certain risk characteristics, are more likely to use smokeless tobacco. In fact, in Sweden, it was a prevalence odds ratio of 11.7 compared to females. And that is translated to males being less likely than females to ever smoke or to be exclusive smokers. And, again, this was based on national survey data.

So you've got a population that may be prone to tobacco use at some time, and it appears that if

they go down the road of smokeless tobacco versus cigarettes, then they're less likely to be cigarette smokers later on, something that you can see in the Swedish data and you can see in the U.S. data as it's starting to happen.

So the gateway effect in the U.S., again, this data has just started to develop, but this is an important slide because as you go through and start critiquing these studies, there has been a lot of debate in the literature about how you interpret these studies.

So what I'm going to do is point out some of the deficiencies in these studies. While I agree with the summaries, these are not arguments that I'm specifically making. They're what other authors are making against these authors.

So for Rodu and Cole, they looked at smokeless initiators and found that they were significantly less likely to be current or daily smokers compared to cigarette -- I'm sorry -- smokeless initiators significantly less likely to be current or daily smokers compared to

cigarette initiators in national survey. That was the NSDUH over about three different reporting cycles.

Tomar reported that smoking prevalence was higher among smokeless tobacco users. Now, they reported the opposite for adults, but that's not the issue here. Just reporting a higher smoking prevalence in people that use ST is an anecdotal finding, at best. It tells you nothing about association. It tells you nothing about causality. It is a testable hypothesis, but if you don't understand product order, then you can't look at causality, and that's what some of these studies are advocating that must be done.

The ones that have gone through and looked at the national survey data in the U.S. have found that when you look at product order, 20 to 30 percent of smokers could ever be causal from smokeless tobacco use, because the remaining 70 or 80 percent of the population either never used smokeless or used cigarettes before smokeless. And studies that don't look at that association have

the potential to give biased results.

Timberlake adjusted for baseline differences in risk factors for smoking using propensity scoring and found no association with smokeless tobacco use and smoking initiation in a national adolescent survey.

The reason this is important is, as I said before, we understand that there are certain risk factors for tobacco use, and when you do your comparisons of smoker tobacco users versus never tobacco users, you need to start from the same pool, that same pool of risk-takers; otherwise, there's bias in the analysis. And Timberlake actually called into question the Severson finding, which was a regional adolescent cohort, Oregon boys, I think, seventh to ninth grade, that didn't take that kind of precaution when they did their regression analysis.

Then O'Connor 2005 and 2003, they adjusted for these non-causal users; in other words, taking someone out of the analysis that never used ST or used cigarettes first, as well as known predictors

of smoking. And they found that smokeless use was not predictive of current smoking. In that analysis, the 2003 paper was specifically a re-analysis of Tomar 2003. And O'Connor concluded that the Tomar 2003 should not be used as any evidence of a gateway effect.

So, again, I point these papers out. This dialogue and critiquing of some of these data is all out there, and it's good reading.

So moving into the last part of the talk, and that is what can we learn from population models, and that was something that I think was important in the menthol dialogue, if I can call it that.

The life tables method was used early on to estimate differences in health-adjusted life expectancies and net population harm for different exposure conditions. So the Gartner work used both U.S. data and Australian data. And I need to point out that life tables do not account for tobacco use trajectories, but instead provide estimates for survival under static exposure distributions. So

there is some limitation with the life tables approach. Nonetheless, there was little difference between health-adjusted life expectancy for switchers compared to quitters or ST users compared to never users.

They did some tipping point analysis. We'd be interested in the impact of certain population level effects or the intended consequences. And as part of that, they found that it would take 17 to 21 potential quitters, that is, smokers that would have quit otherwise if smokeless tobacco wasn't available, it would take that many potential quitters switching to smokeless to offset the health gain from one smoker moving to smokeless.

So at this time, we were developing some of our own population models. We developed a model, a dynamic population model that allowed for accounting of tobacco exposure trajectories and time-dependent effects of exposure and cessation. We were able to confirm these findings, as well as the tipping point analyses. We've written up the paper. It's been presented at an epidemiology

conference, but we haven't submitted it yet.

I think Dr. Benowitz brought up the Mejia paper. We have reviewed the paper. You can see some of my colleagues' comments on tobacco control. It would take three slides to sum up what we thought was wrong with this model.

They looked at the impact of promoting smokeless use as a safer alternative to smoking and suggested no population level benefit. But the model is overly simplistic. There are minimal exposure states and transitions, and it applies the same rates for initiation, cessation and transition to the whole population, and we know that there are gender differences, age differences and such.

Then the health outcome, which was based on the health index, was assumed to be the same regardless of duration of tobacco use or cessation. So if you were a smoker, regardless of how long you were a smoker, if you ever quit, you carried the same health risk.

Again, there are data for these inputs that could have been used, and the model output is only

as good as the input. On top of that, the initial exposure distributions and transition probabilities are very difficult to justify. For example, they assume that smokeless tobacco users were very unlikely to quit and very likely to switch to smoking or dual use, which are both deficits, population level deficits associated with smokeless tobacco use. On the other side, they assumed that smokers were very likely to quit or switch to smokeless and unlikely to initiate dual use, which are both population level benefits.

There was only one way that this model was going to turn out with that kind of biased assumptions going in. We took their model, which was available on an Excel spreadsheet that was provided through the journal, and made a slight modification, one modification in the transition probabilities, just making them more realistic based on age, and we got a significant population level benefit. This is all detailed in the tobacco control website. The comments are probably 10 pages long, and they go into more detail than

this.

So I described some of our early work with population level models. Through a grant, we continued this work on the outside of the company, trying to make a model that would be informative to public health for hypothesis testing. And we have a model now, which we just presented at the American College of Epidemiology or North American Congress of Epidemiology, I'm not sure which. But it's a dynamic model that estimates the impact on tobacco-related mortality with increased prevalence of a reduced risk product, whether it's a snus, whether it's a dissolvable. If you understand relative risks or have some inputs to put in, you can model anything.

It takes a hypothetical population, what we use is one million 12-year-olds at start, of never smokers and follows them to an end age, which is usually 72. You have up to 33 different transitions into and out of tobacco smoke -- I'm sorry -- tobacco exposure. So you can have someone that initiates with smokeless and goes to

cigarettes, relapses and goes back to cigarettes and then to smokeless. I mean, we have 33 transitions that you can follow.

Now, for the hypothesis testing, you don't have to use them all, and that's easy to do, depending on what you want to look at. Unlike the Mejia model, the mortality is based on age, duration of smoking, and duration of cessation, specific person years and deaths from a population of interests.

At the end of each category, age category, and, again, those are user-defined, as well, we use it in five-year intervals, you get an estimate of the number of survivors, assuming that a risk reducer product was not available and the difference between that and one that you assume some user input prevalence of a smokeless product or a reduced risk product.

The whole model was implemented on WinBUGS, which allows an estimation of variability for the model outputs, as well as inputs. We didn't think it was appropriate to just spit out one number.

So the next thing we did is validate these models. For the base case, which is no smokeless tobacco use or very little prevalence in the population, we compared against the U.S. population. We used transition probabilities based on U.S. smoking initiation and cessation rates from 1980 and followed them through about 2006. We used a conservative excess relative risk of .11 for smokeless tobacco compared to cigarettes.

As we reach back, at the beginning of the talk, I talked about the Levy expert panel consensus. Relative risk is 5 to 10 percent. We used 11 percent, which was the highest number that was provided in their publication. And the coefficients for mortality were based on data from the Kaiser Permanente cohort.

So when we run our model with a number of these assumptions and data inputs, our base case model projects 672,000, approximately, survivors through this time interval compared to the U.S. life table, which is 674. So we feel like our base case model has been validated.

For the full model, and that is a model that accounts for some level of prevalence of a reduced risk product use in the population, we used the Swedish data and compared it to the Swedish life table. So, again, the transition probabilities were based on Swedish data, adjusted to approximate tobacco use patterns in the early 1980s. The coefficients for mortality were based on the KP data, because we couldn't find a corresponding dataset in Sweden, but we did adjust for differences in background mortality between the U.S. and Sweden. The full model estimated that there were 759,000 survivors in our full case model compared to 764,000 in the Swedish life table based on Swedish statistics data.

Then we went to hypothesis testing, and the first question we asked was if you could take the Swedish transition probabilities starting in 1980 and apply them to the U.S. population, what would have been the result. We already know that smokeless tobacco use in the U.S. is very low. But if we use these same assumptions for low

nitrosamine smokeless tobacco, we apply the Swedish transition probabilities, what would be the result?

So for the transition probabilities, the rates that we use, and all the rates are very transparent, smoking initiation versus remaining never tobacco user, 5 percent; smokers switching to smokeless versus quitting, 2 percent; smokeless initiator switching to smoking or dual use, 1 percent or 3 percent; and then smokeless initiators remaining smokeless or quitting, 70 percent and 19 percent. These are based on Swedish data. I think it's the Lundqvist 2009 analysis.

Again, we continued to use the conservative excess relative risk of .11, when, scientifically, we could have used a much lower number. The life tables were through 2006, and, again, the model starts with one million 12-year-old never users. So this is not representative of tobacco users; it's the whole population.

When we run this analysis, we see an estimated 19,340 lives potentially saved in the U.S. if the tobacco use in the U.S. had been

similar to the pattern of Sweden starting in the 1980s.

So towards the power of the model, we can look at a number of counterfactuals, and we can look at them all at the same time. If you look at this -- and it may be difficult to read, so I'll just point out some things. Everyone has it in front of them and I can answer questions on it.

But if you were to look at some of the things that have been raised as unintended consequences, what public health is worried about -- and, that is, if we looked at increased smokeless tobacco use versus remaining never users -- and we doubled that number from 5 to 10 percent -- if we increase the number of smokers switching from smokeless instead of quitting, if we increase that fivefold, and if we increase the ST initiators switching from smoking or dual use from 1 percent to 3 percent to 20 percent, and we combined all those unintended consequences, the benefits that we saw with converting the Swedish transition probabilities to the U.S. population of

19,340 deaths would only be reduced to 17,730 deaths.

If we took all those things and combined them with a number of things that have to do with quitting and relapse, all of them being population level deficits, all of them defined here, we combined all those things, with changing the estimated relative risk from .11 to .5, which is much, much higher than anyone would ever suggest, you still have a net save of almost 13,000 lives; although if you look at the posterior interval, you now have statistical balance there. These data would be barely statistically significant or different than no effect.

Then if you look at a net population benefit, and that is a reduction in smokers that continue to smoke or switch to ST or switch to dual use, you can move that number, again, not that much, but from 19,000 to 30,000.

So the estimates from the population model indicate a population benefit with increased smokeless use and really minimum impact for the

counterfactuals, and that is because the relative risks for smokeless tobacco, like dissolvable products, compared to cigarettes are so much less.

So, to summarize, the dual use of smokeless tobacco products, for example, low nitrosamine smokeless tobacco products, and cigarettes are not associated with an increased risk of disease compared to exclusive smoking. This is consistent -- in other words, you must consider the comparative disease risks to properly examine the nature and impact of smokeless tobacco products on public health.

Dual users are more likely to reduce versus increase smoking frequency, and thereby reduce exposure to smoke toxicants. As was pointed out or suggested in one of the publications by O'Connor, the substitution patterns are consistent with smokers preferring a gradual shift rather than an immediate changeover for quitting similar to NRTs. And I think some of the early data out there suggest that there is a period of dual use. This is not -- for some, it may be an immediate

changeover, but it takes some acquiring to these products. New users are more likely to quit smoking compared to exclusive smokers, and smokeless tobacco users are less likely to initiate smoking; if you will, a gateway away from smoking.

The population models estimating changes in tobacco-related mortality indicate a net population level benefit with increased smokeless tobacco use and really provide what I think will be necessary insight to the counterfactuals.

Now, the model that I discussed, we developed outside the company, and it resides with some of our outside collaborators. We developed that model for public health, for public health to use for hypothesis testing, and it's our intention to make that model available for this hypothesis testing.

I think the only caveat we would have is that as people use the model, they are transparent with the inputs they use. The only way we can evaluate how the model is being used or compare one study versus another is if we understand the

plausibility of the inputs.

The last slide. I will point out that these current trends we see in the U.S. and Scandinavia are occurring despite a misconception, a significant misconception, regarding the comparative risks associated with smokeless tobacco and cigarettes. A vast majority, approximately 85 percent, of U.S. tobacco users incorrectly perceive that the disease risks associated with smokeless tobacco are similar or greater than that of cigarettes, when nothing could be further from the truth.

I cited O'Connor here, but there are three or four papers that have looked at this. Their summary was this represents a major public health failing. It is the nicotine -- I'm sorry. Nicotine in tobacco products, while addictive, is not considered a significant threat to health. Instead, it is the smoke that is inhaled from burning tobacco that poses the most significant risk for disease. This misconception regarding the comparative risks associated with smokeless tobacco

and cigarettes has the potential to adversely impact public health, because it undoubtedly drives tobacco use behaviors.

Then the last five or six slides are all the references that we used to put this together. And my apologies. It looks like I ran over a little bit. I wanted to go through some stuff to make sure that it was understood.

DR. SAMET: I think we're fine on time, and I think we have time to discuss your presentation. Thank you.

I think just as a general comment, and I think this is really directed at the committee. We heard a lot of information about smokeless tobacco use. Just as a reminder, our charge is dissolvables. And I think the question that we will have to sort through is, in fact, sort of what are the lessons learned out of these smokeless tobacco literature that may be transferrable to the dissolvables and what are the criteria for, in fact, extrapolating these lessons learned to our task. And I think that's going to be challenging

since there's a sparsity of data, as we have seen, for dissolvables themselves, by the very nature of the natural history of these products.

So thank you. Let me open it up.

Patricia?

DR. NEZ HENDERSON: Throughout your presentation, I was thinking about tobacco policies that had been put in place both in Europe, as well as here in the United States. Was that considered at all in any of, I guess, the papers that you looked at or any of the studies?

DR. CURTIN: Was that considered at all?

DR. NEZ HENDERSON: Yes.

DR. CURTIN: You mean the existing policies of reducing initiation, increasing cessation, those type policies.

DR. NEZ HENDERSON: Right. Like smoke-free policies.

DR. CURTIN: Oh, sure. That's a common thread through this debate. For those that would argue that tobacco harm reduction should be added to those policies, because maybe those policies

have taken us to a certain extent -- in other words, it would appear that current prevalence of smoking in the U.S. has kind of bottomed at about 20 percent. Some people have argued that we've hit a population of hardcore smokers and that there may be something else needed to continue that decline that was so prevalent for a couple decades; that advocating switching from a more risky product to a less risky product, such as smokeless tobacco, such as snus, such as dissolvables, may be what's needed to keep those trends going down.

So, yes, I think people always recognize that those are things that have dramatically reduced smoking in this country over the past several decades. But this may provide an opportunity, continued with those opportunities that already exist.

I think the debate has been when we apply decreased initiation or increased cessation to all tobacco products, regardless of their risk, that's when we confuse smokers. When they don't understand that it's the smoke that causes disease

versus the nicotine or something else in tobacco, that's when people don't make informed choices and it's difficult to drive those numbers farther down.

DR. SAMET: Neal?

DR. BENOWITZ: First, it sounds like the scenario that you're developing is one in which dissolvables are promoted to be used instead of smoking, and not the sustained smoking. But that's not how your product is being marketed now. Right? So it assumes -- that's marketed differently. And I think marketing is really going to be important in terms of how the product is used, both explicit and implied marketing.

So this model is really different from how you're currently marketing, which is for people who are smokers who -- when they can't smoke.

DR. CURTIN: So, okay. I guess I'm trying to understand your question. How is the model different, because while the Mejia paper looked at motive to quit or at least intended to, it really doesn't play into the model. At the end of the day, any model is based on transition

probabilities. So what the intention is may be interesting, but it's the transition probabilities and what happens. So that's with respect to the model.

Now, with respect to what these products could be used for, Reynolds is dedicated, intending to provide lower risk alternatives to smokers and other tobacco users that want to continue to use tobacco products.

Once we were under regulation and we couldn't talk about relative risk. We didn't know exactly where to go. That's a big limitation. When you've got this huge difference in risk for smokeless and cigarettes, not being able to talk about that, how do you enlist people to try your product?

So I think what Dr. Williams said is in the marketing that's going on now for the dissolvables, we are advocating to people to switch, and that is not use it when you can or use it when it's convenient, but to switch. And we started that with snus at the end of last year in a New Year's

campaign and then continued that this year with the New York smoking ban.

So the company is making the transition to raising awareness in the products to now asking smokers to make an action, and that is consider switching to these products.

Again, we're still hamstrung by not being able to talk about relative risk.

DR. BENOWITZ: And I understand that, and I think it's an important point. My only point is that in the end, these transitions are going to be influenced substantially by how the product is marketed.

DR. CURTIN: Sure.

DR. BENOWITZ: And so I think it's something we need to certainly keep in mind.

DR. CURTIN: I'm sorry. I don't mean to interrupt. But that's kind of my point of the last slide. We're seeing some favorable transitions now in a world of misunderstanding. I mean, any kind of reductions in risk or disease or mortality for current tobacco users is good for everybody, the

consumer, public health, the companies.

If you really want to move these transitions, based on marketing, give smokers accurate and reliable information. If they understood the difference in risk, they may be willing to give up a little of sensation or taste or what have you if they would still get their nicotine or whatever they get out of their tobacco product and could still use that tobacco product, but reduce the risk at the same time.

DR. BENOWITZ: I understand that. The other thing, which is just sort of a request, I had tried to follow the assumptions of transitions as well as I could, but it was difficult. It would be really nice if we could get a full copy of the paper and all the documentation for the transitions so we could look at it.

DR. CURTIN: Okay. So I'm not sure if it happened, but our intent was to put a copy of the poster -- fair enough, fair enough. The hypothesis testing wasn't in the poster. So we've got a manuscript that is incredibly true to that poster.

If you read the poster, you've read the manuscript.

In the journal that we're working with, they would like a complementary manuscript on hypothesis testing. That's what this work was done for. Once that manuscript is developed, and I would say it's going to be in August sometime, and they're ready to submit, we would be happy to make those available to FDA.

That includes -- we've got a thick packet of all the probabilities, the assumptions that went in. We want to be very transparent with this. Compared to anything else out there, it's an incredibly powerful model, and I wish I could take even 1 percent credit for it. But we really did work with some people that were really on top of their game in terms of modeling, and we want to make it available to public health. We think it'll be important for hypothesis testing not just on dissolvable tobacco, but other products, as well as getting some insight into what would be the tipping point for an unintended consequence. Is there any number of non-users that would have to start using

smokeless tobacco at 3 percent of the risk of smoking to where it would ever be an issue? And those are some of the hypotheses you can test that were done by Gartner with a much more simple model.

DR. SAMET: Just as a question. When you say make the model available to public health, are you going to post the model so that it's generally available to anyone who wants to use it, available on request, or perhaps you don't know yet?

DR. CURTIN: Don't know yet. I mean, we don't know yet, and we've reached out to some IT people to figure out the best way to do this. And they've never done anything like this, so we haven't figured it out. Now, again, we would want to publish the data before we make it available, but that doesn't mean that you couldn't work with our colleagues at Environ and Colorado State and propose a list of questions or a list of scenarios that you would want tested, and we could do that for TPSAC or for FDA.

We want to get the model at least submitted. How we're going to make it available to public

health, we're open to suggestions. We've never done anything like this. They've never done anything like this. So we don't know exactly how to do that.

DR. BENOWITZ: What I'd like to see just as a starter, without even the model, is just seeing all the documentation for the transition assumptions.

DR. CURTIN: And I provided some of those, and if you will look in the counterfactual page, you'll see what we changed those to.

Now, in the poster, I think it lists some of what we used as our transition probabilities. I mean, I did show them, and you can see that they're not out of bounds. They're not even that different from the U.S., in my mind, on some of them. But you're talking about over a 25-year period and a small change can be big.

DR. BENOWITZ: I just want to see the data behind the transition assumptions.

DR. SAMET: I think he's asking, as you've made these assumptions, on what basis did you make

them and what are the references for those.

DR. CURTIN: What we did is -- we didn't make them up out of whole cloth. We point to particular or specific papers. I hope that's in the poster, but if not, we'll provide that.

DR. BENOWITZ: Thanks.

DR. SAMET: Let's see. Bob?

DR. BALSTER: Just a very quick question. So the number you're showing of approximately 20,000 saved lives using the assumptions from the Swedish, over what period of time would that life savings occur?

DR. SAMET: Cohort. That was --

DR. CURTIN: 1980 to 2006, if I recall correctly.

DR. BALSTER: I see.

DR. CURTIN: But keep in mind this is not 19,000 per 300 million people, and it's not even 19,000 per 45 million tobacco users. This is 19,000 people in an experimental population of one million.

DR. BALSTER: Okay.

DR. CURTIN: If you wanted to extrapolate that out, there's 300 million people in the U.S. -- again, this is a hypothetical population.

DR. BALSTER: I understand that, right.

DR. CURTIN: Twelve-year-old never users on through.

DR. SAMET: Just to make sure I understand, I thought you said that this is your cohort of a million lives, premature deaths avoided up to age 72.

DR. BALSTER: That's what I thought, too.

DR. SAMET: That's not what you just said.

DR. CURTIN: What we did is we started with a million 12-year-olds and followed them from age 12 to 72, putting on these transition probabilities.

DR. SAMET: Fred?

DR. PAMPEL: Another quick question. So these are based on transition probabilities in Sweden in 1980.

DR. CURTIN: Correct. We wanted to go back -- I mean, if you run the model, you can't

make everything happen in a year, and you want to give enough time for people to move in and out of smoking or in and out of ST use. So we moved back to 1980 and then projected forward to where we are now. We didn't do 50 years, but we had to do a number of years to where you would actually see some kind of manifestation of disease over a period of time.

DR. PAMPEL: Use of snus was relatively low in 1980 compared to --

DR. CURTIN: In this country, it was nonexistent. But in Sweden, it was --

DR. PAMPEL: About 10 percent, according to your chart.

DR. CURTIN: About 10 percent.

DR. PAMPEL: Now it's 25 or 30 percent.

DR. CURTIN: It has doubled and it's even higher than that now. And I didn't point it out, but the smoking prevalence for Sweden, I think among younger males, has now gone down either to 10 percent or below 10 percent, and the Swedish snus has continued to go up. And we're starting to

see the same phenomena in Norway, right next door.

DR. PAMPEL: I just wondered. The transition probabilities might change drastically as the composition of snus users changes over the last --

DR. CURTIN: Sure. We could have moved to a time when it was changing more rapidly, but we had decided we needed X number of years. We went back to 1980. We had good data for there. It took some readjusting of the data because we couldn't find comparable data in Sweden that we have in the U.S., which is why I used the Kaiser Permanente cohort data. But I can't remember how much detail is in the poster, but we go through that.

DR. SAMET: David?

DR. ASHLEY: I've got a question that refers back to the presentation I made and the points we were looking for.

Do you guys have any data on whether smokers who start using your dissolvable tobacco products were actually switched completely to dissolvable use?

DR. CURTIN: I don't think we have any data on that. I'm not aware of any data on that. Again, there were three lead markets for a couple years; as Dr. Samet pointed out, low penetrance.

We've been in the new markets for maybe three months. As Dr. Williams said, I think it's going to be 6 months, 9 months, 12 months before we really understand what's going on. And if we don't have a lot of people using these products, then trying to make conclusions about what's going on for a stratification from that data might be somewhat difficult. And that's why given that these products are low nitrosamine smokeless tobacco products, we've looked at that as an example of what has happened in Sweden and what might be happening in the U.S.

I mean, I would have loved to have gotten up here and talked only about dissolvable, but we just don't have that data. And even the data on smokeless is just starting to develop in this country. If we had maybe a national distribution and we were collecting data, maybe, but in two

cities, I think that's going to be a difficult question to answer in the near time.

DR. ASHLEY: So you haven't done any experimental studies where you've taken a group of people, given them dissolvables, see if they would switch over to dissolvables.

DR. CURTIN: I am not well versed in any clinical studies we've done. My understanding is any clinical studies we have done would have been submitted to the FDA, I think, at the March 31st, 2010 submission and would likely be updated with the submission I think that's going to be happening sometime in August or September. But I'm not aware of those data and, again, they would be small numbers of people.

DR. SAMET: I was actually going to make the obvious observation that the surveillance needs here are becoming very complex around sort of the diversifying marketplace of products, and, actually, following individuals, a critical study would be fun, but I think, obviously, we'd like to know what's really going on in the world.

Some years ago, I wrote a paper for NCI with Scott Zeger on the need for sort of serial cohorts within the population, and I think that's probably something that will have to be thought about. And I think, again, when we think about recommendations we might be making nine months from now, I think surveillance will -- the surveillance needs we'll need to figure in. I think it's becoming more and more challenging to think about how to do those.

Let's see. Patricia?

DR. NEZ HENDERSON: I have a question. I guess my concern right now is populations that are at high risk for diabetes and how these products are going to impact their risk, because we're finding out it increases the risk for development of diabetes. So whether their risk will increase, like African Americans and American Indians. Those are the subpopulations that I'm thinking about.

DR. CURTIN: Yes. I'm not aware of what the increased risk of diabetes or contribution to diabetes would be with the smokeless tobacco products. I know that we just went through and did

a review of all the major disease states, and my part was the major diseases, going all the way to the gastrointestinal cancers, from pancreatic cancer, stomach cancer, all that. I didn't look at diabetes. I know it was addressed, and I know that with conclusions, the risk for diabetes or complications with diabetes was significantly lower for smokeless compared to cigarettes. What I can't tell you is if there was any increased risk relative to never users because I just don't remember that data. It doesn't mean I can't get back with you on that, but I know that we have thoroughly researched all the literature on this. For example, I can tell you there are 41 papers on oral pharyngeal cancer. I just don't remember the diabetes, but we can get there.

Dr. Ashley, in response to your question, I think we might be able to address it somewhat on what we've done internally, if you're still interested.

DR. SAMET: And, Mark, do you have questions?

DR. CLANTON: No questions.

DR. SAMET: Do you have any questions? Oh, he said no. Okay. All right.

Neal?

DR. BENOWITZ: As a total change of subject. There was a document that we received from the Virginia Foundation for Healthy Youth which stated that 39 percent of minors believed that Camel Orbs were not tobacco products, but were mints or gum, and 28 percent said that they would try Camel Orbs -- these are non-smokers -- based on packaging.

I was just curious to get your response to that.

DR. CURTIN: I know nothing of the study. I don't know how large it was. I don't know what was included. I mean, I have no idea.

I did appreciate what Dr. Wright pointed out in that it is interesting that these arguments are made for the tobacco products, yet the NRTs, in my opinion, look much more like candy and the packaging looks more like candy packaging.

I'd be happy to take a look at that study and get back to you, but I don't know how many people they looked at. I don't know how the questions were asked.

In my opinion, the packaging is very nondescript and the changes that we've made have made it look more like a traditional product. And when you look at the products themselves, the Sticks, the Strips, the Orbs, I just don't see how they look like candy. And for those of us who use tobacco, it doesn't have the best taste, either.

So I appreciate that there's concern for accidental poisonings, but I think the company has gone a long way to try to prevent that or to make avenues where information is provided if that's happened.

I was at a public health meeting a couple years ago and I walked into a session and everyone was in the back trying to get the packages open, because no one could open them. Luckily, there was a couple of us at the meeting and we showed them. So at some point before we made the changes, they

weren't just child-resistant, they were adult-resistant. I mean, they were that difficult to get into.

DR. SAMET: Did you want to make a comment?

DR. OGDEN: Yes. Our understanding was that we would be able to answer questions as a panel with myself included. So back to Dr. Ashley's question, and I believe Dr. Williams may have a comment to Dr. Henderson's question.

On the clinical trials, as you know, we've presented summary information on a number of clinical trials that we've conducted with smokeless tobacco in general and specifically on dissolvables that has some of that information in it.

We would be very happy to come back to FDA and talk in more detail about it. But at a high level, again, within the confines of the clinical trial, small numbers of subjects, limited duration, there are some smokers who successfully migrate completely to dissolvables, and you see the expected reduction in toxicant exposure as measured by metabolites and biomarkers, et cetera.

So we do have that data. We have a number of trials ongoing. So we'd be happy to provide you more of that information, if that would be helpful, perhaps in response to Dr. Henderson.

DR. WILLIAMS: Yes, real quick. On the dissolvables makeup and sugar content for diabetes, we do use an artificial sweetener in there, sucralose. So we did run caloric content, and it is -- I forgot the numbers, but it's only like 1 calorie or 2 calories. So the caloric content and sugar content are minimal in those products.

DR. SAMET: Okay. Thank you.

Any other questions? David? No. Are there other questions or comments?

[No response.]

Adjournment

DR. SAMET: Okay. Thank you for your presentations, and thank you, also, to Dr. Wright and Star.

Let's see. We are done. I just want to remind everyone that tomorrow we start at 8:00. And for those members of TPSAC staying at the

hotel, that means a shuttle at 8:00 will not get us to the meeting at 8:00, and we'll make sure there's a shuttle at 7:30 one way or another.

So thanks to everyone, and I guess we are launched on dissolvables.

(Whereupon, at 5:15 p.m., the meeting was adjourned.)